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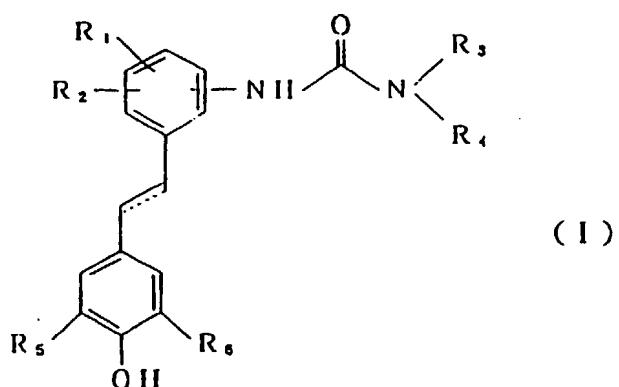
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㉒ Urea derivatives and their use as acat inhibitors.

㉓ Urea derivatives of formula (I)



wherein the valuable groups are as defined in the specification, which possess both an ACAT inhibitory activity and an antioxidative activity. Those derivatives are useful in the prophylaxis and treatment of hypercholesterolemia and atherosclerosis.

FIELD OF THE INVENTION

This invention relates to new urea derivatives, processes for their preparation and their use in medicine. More particularly, the invention relates to compounds having an inhibitory activity against an acyl coenzyme A cholesterol acyltransferase (called hereafter ACAT) and having a protective ability against an oxidative modification of low density lipoprotein (called hereafter LDL).

BACKGROUND OF THE INVENTION

10 In recent years, an interest has been directed to the relationship between an increase in the level of cholesterol in the serum and a human health condition. It has been pointed out that the level of cholesterol in the serum is associated with the amount of cholesterol deposited in the blood vessel system and the deposition of cholesterol in the blood vessel system brings about e.g. lesion of coronary artery, which is responsible for ischemic heart disease.

15 Drugs for reducing the level of cholesterol in the serum have been developed. These drugs, however, were effective in controlling blood cholesterol to an appropriate level, but ineffective in inhibiting absorption of cholesterol from the digestive tracts and deposition of cholesterol on the wall of blood vessels.

ACAT is an enzyme that catalyzes the synthesis of cholesteryl esters from acyl coenzyme A and cholesterol and plays an important role in metabolism of cholesterol and its absorption from the digestive tracts. It is believed that ACAT occurs in the site of mucosa cells of the intestinal tracts and is active in esterification and incorporation of cholesterol derived from the diet. On the other hand, the cholesterol deposited on the wall of blood vessels is the esterified cholesterol. The cholesterol accumulated in the foam cells which plays an important role in the formation of atherosclerosis lesion is also esterified cholesterol. The enzyme that catalyzes the esterification of cholesterol in these sites is also ACAT.

25 Accordingly, the inhibition of an ACAT activity can result in inhibiting the incorporation in vivo of cholesterol derived from the diet and further the formation of cholesteryl ester in specified cell sites.

Compounds having an ACAT inhibitory activity are disclosed in EP 0450660 A1 and EP 0477778 A2. However, those known compounds have only an ACAT inhibitory activity and give no effect on the oxidative modification of LDL causing the foam cell transformation of macrophage which is an important phenomenon for the formation of atherosclerosis lesion.

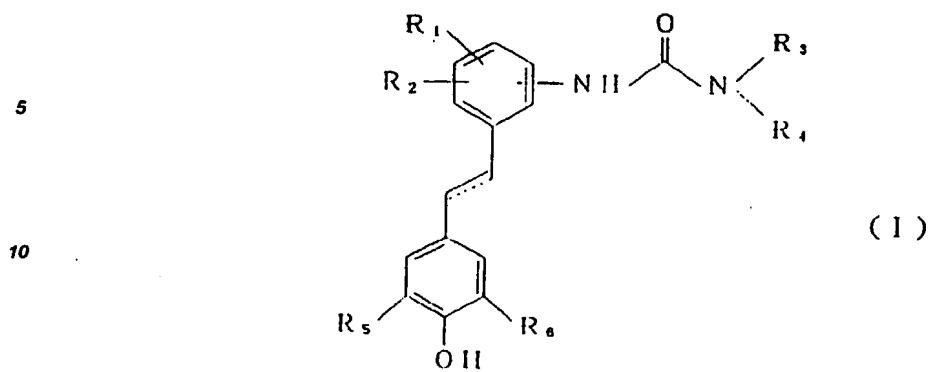
30 The foam cells which play an important role in the formation of atherosclerosis lesion are a product of uptake of oxidatively modified LDL into macrophage which results in the foam cell transformation of the macrophage. It is reported by Diane W. Morel et al. (Atheroma, Vol. 4, pages 357-364, 1984) that, the oxidatively modified LDL causes foam cell transformation of macrophage and plays an important role in the formation of atherosclerosis lesion. A report of TORU KITA et al. (Proc. Natl. Acad. Sci. USA, Vol. 84, pages 5928-5931, 1987) demonstrates that prevention of the oxidative modification of LDL induces regression of the atherosclerosis lesion. Therefore, inhibition of the oxidative modification of LDL, in addition to the above-mentioned ACAT inhibitory activity, is very important in preventing the formation and progression as well as inducing regression of atherosclerosis lesion.

35 40 Under such circumstances, it has been desired to develop the compound having an ACAT inhibitory activity and being capable of inhibiting an oxidative modification of LDL or the like, since such compound may decrease the serum cholesterol level and inhibit the oxidative modification of LDL cholesterol deposited on the blood vessel or tissue, thus being effective for inhibiting the formation and progression of atherosclerosis lesions and inducing its regression.

45 DETAILED DESCRIPTION OF THE INVENTION

We have now found new urea derivatives which exhibit both an ACAT inhibitory activity and an antioxidative activity. The urea derivatives of the present invention possess an ACAT inhibitory activity, thereby inhibiting an absorption of cholesterol from the intestinal tracts, lowering a blood cholesterol level and inhibiting an accumulation of cholesteryl esters in the wall of blood vessels, atheroma and macrophage, and simultaneously an antioxidative activity i.e. a protective activity against the oxidative modification of LDL which participates in foam cell transformation of macrophage thereby effectively inhibiting the formation and progression of atherosclerosis lesion and inducing its regression.

50 55 According to one aspect of the present invention, there is provided a compound of formula (I) and pharmaceutically acceptable salts thereof, which exhibits both an ACAT inhibitory activity and an antioxidative activity.



in which:

17 R_1 and R_2 , which may be the same or different, each represents
a hydrogen atom,
a halogen atom,

20 a straight or branched (C_1 - C_6)alkyl group or
a straight or branched (C_1 - C_6)alkoxy group,

25 R_3 and R_4 , which may be the same or different, each represents
a hydrogen atom,
a straight or branched (C_1 - C_{12})alkyl group,

30 a straight or branched (C_2 - C_{20})alkenyl group,
a (C_1 - C_6)alkoxy(C_1 - C_6)alkyl group,
a (C_1 - C_6)alkoxycarbonyl(C_1 - C_6)alkyl group,
a benzyloxycarbonyl(C_1 - C_6)alkyl group in which the alkyl moiety is optionally substituted by phenyl,
a N,N-di(C_1 - C_6)alkylamino(C_1 - C_6)alkyl group,

35 a N-(C_1 - C_6)alkyl-N-benzylamino(C_1 - C_6)alkyl group,
a (C_1 - C_6)alkylthio(C_1 - C_6)alkyl group,
an oxo(C_1 - C_6)alkyl group,
a hydroxy(C_1 - C_6)alkyl group,
a dihydroxy(C_1 - C_6)alkyl group,

40 35 a cyclo(C_3 - C_{15})alkyl group,
a cyclo(C_3 - C_6)alkyl(C_1 - C_6)alkyl group,
a dicyclo(C_3 - C_6)alkyl(C_1 - C_6)alkyl group,
a bicyclo(C_6 - C_9)alkyl group,
a tricyclo(C_9 - C_{12})alkyl group,

45 40 in which in all cases the cycloalkyl group or the cycloalkyl moiety is optionally substituted by one or two substituents selected from the group consisting of (C_1 - C_6)alkyl, hydroxy, amino, acetoxy, acetamido, phenyl, benzyloxy, dimethylaminophenyl, and methylenedioxyphenyl, which may be further fused with a benzene ring,

50 45 an aryl group,
an aryl(C_1 - C_6)alkyl group,
a diaryl(C_1 - C_6)alkyl group,

55 50 in which in all cases the aryl group or the aryl moiety is optionally substituted by one, two or three substituents selected from the group consisting of (C_1 - C_6)alkyl, (C_1 - C_6)alkyloxy, halogen, nitro, hydroxy, amino, dimethylamino, methylenedioxy, and pyrrolidinyl,

55 55 a heterocyclic group or
a heterocyclic group attached to a (C_1 - C_6)alkylene chain,

55 55 in which in all cases the heterocyclic group represents a saturated or unsaturated, 5 to 8 membered ring monocyclic or bicyclic, heterocyclic group containing 1 to 3 heteroatoms selected from the group consisting of S, O and N, and the heterocyclic group is optionally substituted by one or two substituents selected from the group consisting of acetyl, hydroxy, (C_1 - C_6)alkyl, (C_1 - C_6)alkyloxy, cyclo(C_3 - C_6)alkyl, cyclo(C_3 - C_6)alkyl(C_3 - C_{10})alkyl, pyridyl(C_1 - C_6)alkyl, phenyl, phenyl(C_1 - C_6)alkyl, diphenyl(C_1 - C_6)alkyl, and phenylpiperazinyl, the phenyl group or the phenyl moiety being optionally substituted by one or two substituents selected from the group consisting of halogen, hydroxy, (C_1 - C_6)alkyl, (C_1 - C_6)alkoxy, cyano, diethylamino and trifluoro-

methyl, which may be further fused with a benzene ring,
and further R_3 and R_4 , together with the nitrogen atom to which they are attached, may form a saturated or unsaturated heterocyclic group,

5 in which the heterocyclic group represents a 5 to 8 membered ring monocyclic or bicyclic, heterocyclic group or a group derived from a heterocyclic spiro compound, which may contain one or two heteroatoms selected from the group consisting of S, O or N, the heterocyclic group being optionally substituted by one or two substituents selected from the group consisting of $(C_1-C_6)alkyl$, hydroxy, hydroxy $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy(C_1-C_6)alkyl$, acetoxyl $(C_1-C_6)alkyl$, $(C_1-C_6)alkylcarbonyl$, $(C_1-C_6)alkoxycarbonyl$, amino, tosyl, phenyl, halogenophenyl, $(C_1-C_6)alkoxyphenyl$, phenyl $(C_1-C_6)alkyl$, benzyloxy, benzyloxy $(C_1-C_6)alkyl$, tolyl, xylyl, benzoyl,
10 methylenedioxyphenyl $(C_1-C_6)alkyl$, pyridyl, pyridylcarbonyl, piperidyl, pyrrolidinyl $(C_1-C_6)alkyl$ and pyrrolidinylcarbonyl $(C_1-C_6)alkyl$, which may be further fused with a benzene ring,
in which in all cases the alkyl and alkoxy moieties may be either straight or branched,
with the proviso that both R_3 and R_4 do not represent a hydrogen atom at the same time;
15 R_5 and R_6 , which may be the same or different, each represents a straight or branched $(C_1-C_6)alkyl$ group;
and the line

20



represents $-CH_2CH_2-$ or $-CH=CH-$.

Referring to R_1 and R_2 in formula (I), the halogen atom includes fluorine, chlorine, bromine and iodine, the $(C_1-C_6)alkoxy$ group includes e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy and hexyloxy, and the $(C_1-C_6)alkyl$ group includes e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl and hexyl.

Referring to R_3 and R_4 in formula (I), the $(C_1-C_{12})alkyl$ group includes e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl, heptyl, octyl, trimethylpentyl, 2,4,4-trimethyl-2-pentyl, nonyl, decyl and dodecyl. The $(C_2-C_{20})alkenyl$ group includes e.g. vinyl, allyl, isopropenyl, 2-butenyl, 2-pentenyl, 4-pentenyl, 3-hexenyl, 5-hexenyl, 4-octenyl, 7-octenyl, 7-decenyl, 3,7-dimethyl-2,6-octadienyl, 10-tetradecenyl, 8-heptadecenyl, 8-octadecenyl and 4,7,10,13,16-nonadecapentaenyl. The $(C_1-C_6)alkoxy(C_1-C_6)alkyl$ group includes e.g. 2-methoxyethyl, 4-methoxybutyl, 2-methoxybutyl, 6-methoxyhexyl, ethoxymethyl, 3-ethoxypropyl, 2-propoxypentyl, 5-propoxypentyl, isopropoxymethyl, butoxymethyl, 2-isobutoxyethyl, sec-butoxymethyl, tert-butoxymethyl, pentyloxyethyl and hexyloxyethyl.

35 The $(C_1-C_6)alkoxycarbonyl(C_1-C_6)alkyl$ group includes e.g. 2-(methoxycarbonyl)ethyl, 7-(methoxycarbonyl)heptyl, 2-(ethoxycarbonyl)ethyl, 4-(ethoxycarbonyl)butyl, propoxycarbonylmethyl, 3-(propoxycarbonyl)butyl, isopropoxycarbonylmethyl, butoxycarbonylmethyl, 1-(butoxycarbonyl)ethyl, 2-(isobutoxycarbonyl)ethyl, sec-butoxycarbonylmethyl, 2-(tert-butoxycarbonyl)ethyl, pentyloxy carbonylmethyl and 2-(hexyloxy carbonyl)ethyl, α -(methoxycarbonyl)benzyl, α -(ethoxycarbonyl)benzyl.

40 The benzyloxycarbonyl $(C_1-C_6)alkyl$ group includes benzyloxycarbonylmethyl, 2-(benzyloxycarbonyl)ethyl, 6-(benzyloxycarbonyl)hexyl, 4-(benzyloxycarbonyl)butyl and α -(benzyloxycarbonyl)benzyl.

The $N,N-di(C_1-C_6)alkylamino(C_1-C_6)alkyl$ group includes e.g. 2-(N,N -dimethylamino)ethyl, 4-(N,N -dimethylamino)butyl, 2-(N,N -diethylamino)ethyl, 3-(N,N -diethylamino)propyl, N,N -diisopropylaminomethyl, N,N -di-butylaminomethyl, 2-(N,N -dibutylamino)ethyl, 2-(N,N -diisobutylamino)ethyl, N,N -dipentylaminomethyl, 2-(N,N -dihexylamino)ethyl and N,N -diisohexylaminomethyl.

45 The $N-(C_1-C_6)alkyl-N$ -benzylamino $(C_1-C_6)alkyl$ includes e.g. 2-(N -benzyl- N -methylamino)ethyl, 2-(N -benzyl- N -ethylamino)ethyl, 4-(N -benzyl- N -methylamino)butyl, 2-(N -benzyl- N -ethylamino)ethyl and 3-(N -benzyl- N -ethylamino)propyl.

The $(C_1-C_6)alkylthio(C_1-C_6)alkyl$ group includes e.g. 2-(methylthio)ethyl, 2-(ethylthio)ethyl, propylthiomethyl, 2-(isopropylthio)ethyl, 1-(butylthio)ethyl, isobutylthiomethyl, tert-butylthiomethyl, pentythiomethyl and hexylthiomethyl.

The oxo $(C_1-C_6)alkyl$ group includes e.g. 2-oxopropyl, 2-oxobutyl, 4-oxopentyl, 6-oxoheptyl and 2-oxooctyl.

The hydroxy $(C_1-C_6)alkyl$ group includes e.g. 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 3-hydroxybutyl and 6-hydroxyhexyl.

55 The dihydroxy $(C_1-C_6)alkyl$ group includes e.g. 2,3-dihydroxypropyl, 4,5-dihydroxypentyl, 1,5-dihydroxy-3-pentyl, 2-ethyl-1,3-dihydroxy-2-propyl, and 2,4-dihydroxy-3-methylpentyl.

The cyclo $(C_3-C_{15})alkyl$ group includes e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl, cyclododecyl, 1-phenylcyclopentyl, 4-(benzyloxy)cyclohexyl, 4-aminocyclohexyl, 4-acet-

amidocyclohexyl, 4-hydroxycyclohexyl, 4-acetoxycyclohexyl, 4-tert-butylcyclohexyl, 2,3-dimethylcyclohexyl, 1,2,3,4-tetrahydronaphthyl, cyclododecyl and benzyloxycyclohexyl.

The cyclo(C₃-C₉)alkyl(C₁-C₆)alkyl group includes e.g. cyclopropylmethyl, 2-cyclobutylethyl, 2-cycloheptyl-ethyl, cyclohexylmethyl, 3-cyclohexylpropyl, 4-cyclohexylbutyl, cyclooctylmethyl, 5-cyclooctylpentyl, 1-(4-dimethylaminophenyl)cyclopentylmethyl and 1-(3,4-methylenedioxyphenyl)cyclopentylmethyl.

The dicyclo(C₃-C₉)alkyl(C₁-C₆)alkyl group includes e.g. dicyclohexylmethyl, 2,2-dicyclohexylethyl and 3,3-dicyclohexylpropyl.

The bicyclo(C₆-C₉)alkyl group includes e.g. bicyclo[3.3.0]-2-octyl, bicyclo[3.3.1]-2-nonyl and bicyclo[3.2.1]-2-octyl.

10 The tricyclo(C₉-C₁₂)alkyl group includes e.g. tricyclo[5.2.1.0^{2,6}]decyl and tricyclo[3.3.1.1^{3,7}]decyl.

The aryl group includes e.g. phenyl, 1-naphthyl, 2-naphthyl, 3-naphthyl, 4-methylphenyl, 2,6-diisopropyl-phenyl, 3,5-di-tert-butyl-4-hydroxyphenyl, 2-methoxyphenyl, 4-hydroxyphenyl, 4-fluorophenyl, 2-nitrophenyl, 4-chloronaphthyl, 3-amino-2-naphthyl, 5-hydroxynaphthyl, 5-methoxynaphthyl and anthryl.

15 The aryl(C₁-C₆)alkyl group includes e.g. benzyl, phenethyl, α -methylbenzyl, 3-phenylpropyl, 4-phenylbutyl, 9-anthrylmethyl, 4-ethylbenzyl, 4-ethoxybenzyl, 4-fluorobenzyl, 3,4-methylenedioxybenzyl, 3,4,5-trimethoxybenzyl, 4-methylphenethyl, 2-methoxyphenethyl, 4-methoxyphenethyl, 3,4-dimethoxyphenethyl, 3-chlorophenethyl, 4-chlorophenethyl, 4-fluorophenethyl, 4-nitrophenethyl, 3,4,5-trimethoxyphenethyl, 4-nitrophenylbutyl, 1-(4-fluorophenyl)-2-methylpropyl, 3-(3,4-dichlorophenyl)propyl, 4-dimethylaminophenethyl, 2-(3,4-dichlorophenyl)-2-propyl, 2-(3,4-dichlorophenyl)-2-methylpropyl, 2-(2-fluorophenyl)-2-methylpropyl, 2-(3-fluorophenyl)-2-methylpropyl, 2-(4-fluorophenyl)-2-methylpropyl and 2-[4-(1-pyrrolidinyl)phenyl]-2-methylpropyl.

The diaryl(C₁-C₆)alkyl group includes e.g. diphenylmethyl, 1,2-diphenylethyl, 2,2-diphenylethyl, 4,4-diphenylbutyl and 6,6-diphenylhexyl.

20 The monocyclic, heterocyclic group includes e.g. 3-furyl, 2-thienyl, 3-pyrrolyl, 2-pyrrolidinyl, 2H-pyran-3-yl, 2-pyridyl, 4-piperidyl, 3-morpholinyl, 2-piperazinyl, 1-methyl-4-piperidyl, 1-benzyl-4-piperidyl, 1-methyl-3-piperidyl, 1-(2,4-difluorobenzyl)-4-piperidyl, 1-(3,4-difluorobenzyl)-4-piperidyl, 1-(3,5-difluorobenzyl)-4-piperidyl, 1-[2,4-bis(trifluoromethyl)benzyl]-4-piperidyl, 1-(4-methoxybenzyl)-4-piperidyl, 1-phenethyl-4-piperidyl, 1-(2-fluorobenzyl)-4-piperidyl, 1-(3-fluorobenzyl)-4-piperidyl, 1-(4-fluorobenzyl)-4-piperidyl, 1-(4-chlorobenzyl)-4-piperidyl, 1-(4-cyanobenzyl)-4-piperidyl, 1-(2-pyridylmethyl)-4-piperidyl, 1-(3-pyridylmethyl)-4-piperidyl, 1-(4-pyridylmethyl)-4-piperidyl, 1-[4-(N,N-diethylamino)benzyl]-4-piperidyl, 1-[bis(4-fluorophenyl)methyl]-4-piperidyl, 1-(4-fluorophenethyl)-4-piperidyl, 1-(2,4-dimethylbenzyl)-4-piperidyl, 1-acetyl-4-piperidyl, 1-(4-hydroxybenzyl)-4-piperidyl, 1-(3,4-dihydroxybenzyl)-4-piperidyl, 1-ethyl-4-piperidyl, 1-neopentyl-4-piperidyl, 1-cyclohexyl-4-piperidyl, 1-heptyl-4-piperidyl, 1-(2-propyl)-4-piperidyl, 1-benzyl-3-piperidyl, 2-phenyl-3-piperidyl, 1-cyclohexylmethyl-3-piperidyl, 1-benzyl-3-pyrrolidinyl, 2-methoxy-5-pyridyl, 2-(4-phenyl-1-piperazinyl)-5-pyridyl and 5,6-dimethyl-1,2,4-triazin-3-yl.

25 The bicyclic, heterocyclic group includes e.g. 3-indolyl, 5-indazolyl, 2-quinolyl, 5-isoquinolyl, 2,4-dimethyl-1,8-naphthyridin-7-yl, 3,9-dimethyl-3,9-diazabicyclo[3.3.1]-7-nonyl, 9-methyl-3-oxa-9-azabicyclo[3.3.1]-7-nonyl, 9-(4-fluorobenzyl)-3-oxa-9-azabicyclo[3.3.1]-7-nonyl, 9-methyl-3-thia-9-azabicyclo[3.3.1]-7-nonyl, 8-methyl-8-azabicyclo[3.2.1]-3-octyl and 1-azabicyclo[2.2.2]-3-octyl.

30 40 The heterocyclic group attached to an alkylene chain may be the above-mentioned monocyclic or bicyclic heterocyclic group attached to an alkylene chain, which includes e.g. 3-furylmethyl, 3-(2-thienyl)propyl, 2-(3-indolyl)ethyl, 2-(3-pyrrolyl)ethyl, 2-pyrrolidinylmethyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 2-(2-pyridyl)ethyl, 2-(4-piperidyl)ethyl, 3-(3-morpholinyl)propyl, 3-indolylmethyl, 2-(5-indazolyl)ethyl, 2-quinolylmethyl, 3-(1-imidazolyl)propyl, 2-morpholinoethyl, 3-morpholinopropyl, 3-(2-methylpiperidyl)propyl, 2-(1-pyrrolidinyl)ethyl, [4-(4-fluorobenzyl)-3-morpholinyl]methyl and (1-benzyl-4-hydroxy-4-piperidyl)methyl.

45 50 55 When R₃ and R₄ in formula (I), together with the nitrogen atom to which they are attached form the heterocyclic ring, the monocyclic, heterocyclic group includes e.g. pyrrolidinyl, 2,5-dimethyl-1-pyrrolidinyl, 3-hydroxy-1-pyrrolidinyl, 2-hydroxymethyl-1-pyrrolidinyl, 2-hydroxyethyl-1-pyrrolidinyl, 2-methoxymethyl-1-pyrrolidinyl, 2-(1-pyrrolidinylmethyl)pyrrolidinyl, 3-pyrrolin-1-yl, 2,5-dimethyl-3-pyrrolin-1-yl, piperidino, 2-methylpiperidino, 2-ethylpiperidino, 3-methylpiperidino, 4-methylpiperidino, 4-piperidinopiperidino, 3,3-dimethylpiperidino, 2,6-dimethylpiperidino, 3,5-dimethylpiperidino, 2,4-dimethylpiperidino, 2-(hydroxymethyl)piperidino, 2-(2-hydroxyethyl)piperidino, 2-(2-acetoxyethyl)piperidino, 3-hydroxypiperidino, 4-hydroxypiperidino, 4-oxopiperidino, 4-aminopiperidino, 4-benzylpiperidino, 2-[2-(benzyloxy)ethyl]piperidino, 3-(benzyloxy)piperidino, 1,2,3,6-tetrahydropyridyl, perhydroazepinyl, perhydroazocinyl, piperazinyl, 4-methyl-1-piperazinyl, 3-methyl-1-piperazinyl, 3,5-dimethyl-1-piperazinyl, 2,5-dimethyl-1-piperazinyl, 4-(2-hydroxyethyl)-1-piperazinyl, 4-pentanoyl-1-piperazinyl, 4-acetyl-1-piperazinyl, 4-p-toluenesulfonyl-1-piperazinyl, 4-benzyl-1-piperazinyl, 4-(3,4-methylenedioxybenzyl)-1-piperazinyl, 4-(2-pyridyl)-1-piperazinyl, 4-nicotinoyl-1-piperazinyl, 4-(1-pyrrolidinyl-carbonylmethyl)-1-piperazinyl, 4-benzyl-1-piperidyl, 4-phenyl-1-piperidyl, 4-phenyl-1,2,3,6-tetrahydropyridyl,

4-phenyl-1-piperazinyl, 4-benzyl-1-piperazinyl, 4-(o-tolyl)-1-piperazinyl, 4-(2-fluorophenyl)-1-piperazinyl, 4-(2,3-xylyl)-1-piperazinyl, 4-(2-chlorophenyl)-1-piperazinyl, 4-(2-methoxyphenyl)-1-piperazinyl, 4-(2-ethoxyphenyl)-1-piperazinyl, 4-(m-tolyl)-1-piperazinyl, 4-(3,4-difluorophenyl)-1-piperazinyl, 4-(4-chlorophenyl)-1-piperazinyl, 4-(3,4-dimethoxyphenyl)-1-piperazinyl, homopiperazinyl, morpholino, 2,6-dimethylmorpholino, thiazolidinyl, thiomorpholino, pyrrolyl, 2-ethyl-1-pyrrolyl, 2,5-dimethyl-1-pyrrolyl, pyrazolyl, 3-methyl-1-pyrazolyl, 4-methyl-1-pyrazolyl, imidazolyl, 4-methyl-1-imidazolyl, 4-phenyl-1-imidazolyl, 1H-1,2,3-triazol-1-yl, 1,2,4-triazol-1-yl, imidazolidinyl, 2-imidazolin-1-yl, pyrazolidinyl and 2-pyrazolin-1-yl.

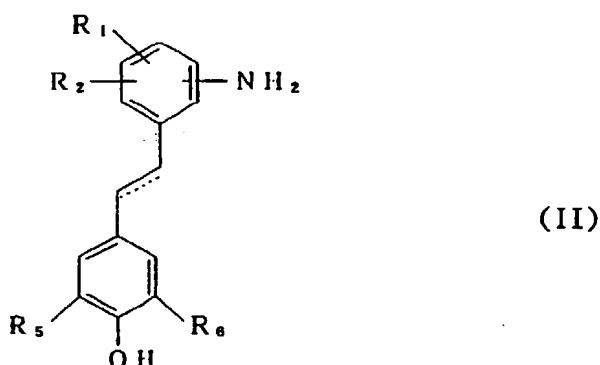
The bicyclic, heterocyclic group includes e.g. 4,5,6,7-tetrahydroindol-1-yl, 1,5,6,7-tetrahydro-4-oxoindol-1-yl, indolinyl, isoindolinyl, perhydroindol-1-yl, decahydroquinolinyl, perhydroisoquinolin-2-yl, 1,2,3,4-tetrahydrocarbazol-1-yl, 1,2,3,4-tetrahydroquinolin-1-yl, 1,2,3,4-tetrahydroisoquinolin-1-yl, 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl, 5H-dibenz[b,f]azepin-5-yl, 10,11-dihydro-5H-dibenz[b,f]azepin-5-yl, 3-azabicyclo[3.2.2]nonan-3-yl, 3-methyl-3,9-diazabicyclo[3.3.1]nonan-9-yl, 3-oxa-9-azabicyclo[3.3.1]nonan-9-yl and 3-thia-9-azabicyclo[3.3.1]nonan-9-yl.

The group derived from the heterocyclic spiro compound includes e.g. 1,4-dioxa-8-azaspiro[4.5]-decan-8-yl, 1,4-dioxa-7-azaspiro[4.4]decan-7-yl, 1,5-dithia-9-azaspiro[5.5]undecan-9-yl and 1-phenyl-4-oxo-1,3,8-triazaspiro[4.5]decan-8-yl.

It should be understood that the compounds of formula (I) include all of their possible isomers including stereoisomer, metabolite, metabolic precursor and metabolic intermediate.

The compounds of formula (I) can be prepared by various conventional procedures as described below.

The compounds of formula (I) are prepared by reacting a compound of formula (II)



wherein R₁ and R₂ as well as R₅ and R₆ are as defined above, and

40

45

denotes -CH₂-CH₂- or -CH=CH- with an isocyanate of formula (III)

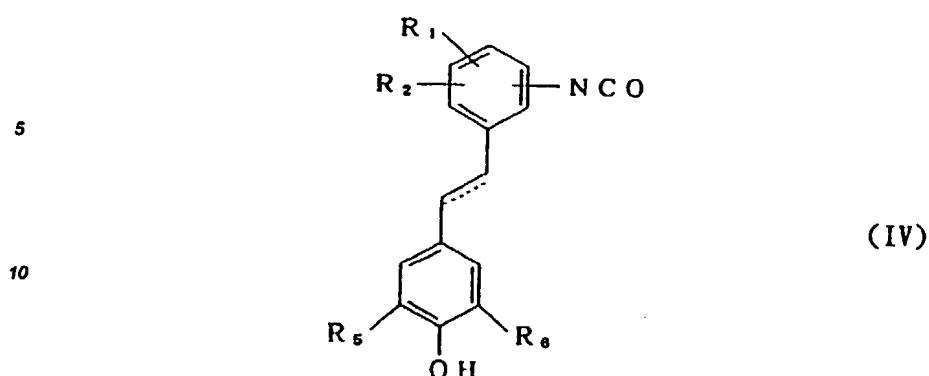
R-NCO (III)

wherein R denotes R₃ or R₄, and R₃ and R₄ are as defined above in an organic solvent under ice-cooling or at a temperature up to room temperature. This reaction is performed using the compound of formula (III) in an amount of 0.1 to 10 moles, preferably 0.5 to 2 moles per mole of the compound of formula (II).

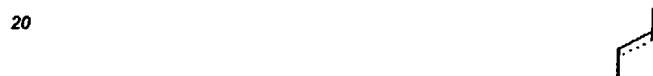
Alternatively, the compounds of formula (I) are prepared by reacting an isocyanate of formula (IV)

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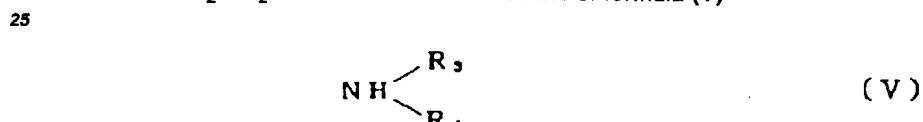
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wherein R_1 and R_2 as well as R_5 and R_6 are as defined above, and

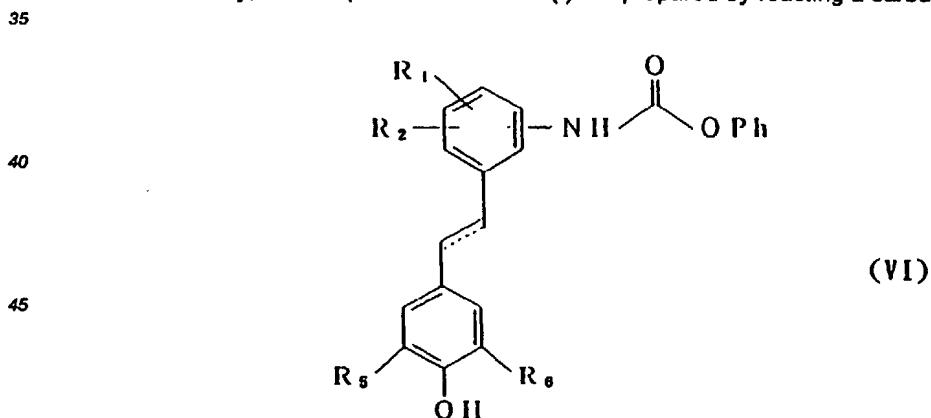


denotes $-CH_2-CH_2-$ or $-CH=CH-$ with an amine of formula (V)



wherein R denotes R_3 or R_4 , and R_3 and R_4 are as defined above in an organic solvent under ice-cooling or at a temperature up to room temperature. This reaction is performed using the compound of formula (V) in an amount of 0.1 to 10 moles, preferably 0.5 to 2 moles per mole of the compound of formula (IV).

Alternatively, the compounds of formula (I) are prepared by reacting a carbamate of formula (VI)



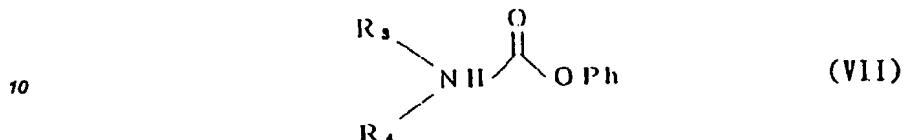
wherein R_1 and R_2 as well as R_5 and R_6 are as defined above, and



denotes $-CH_2-CH_2-$ or $-CH=CH-$ with an amine of formula (V) wherein R denotes R_3 or R_4 , and R_3 and R_4 are

as defined above in an organic solvent while heating at 50-150°C. This reaction is performed using the compound of formula (V) in an amount of 0.1 to 10 moles, preferably 0.5 to 2 moles per mole of the compound of formula (VI).

5 Alternatively, the compounds of formula (I) are prepared by reacting a compound of formula (II) with a carbamate of formula (VII)



15 wherein R denotes R₃ or R₄, and R₃ and R₄ are as defined above in an organic solvent while heating to 50-150°C. This reaction is performed using the compound of formula (VII) in an amount of 0.1 to 10 moles, preferably 0.5 to 2 moles per mole of the compound of formula (II).

20 The isocyanates of formula (III) or (IV) are prepared, for example, by treating a carboxylic acid of formula RCOOH wherein R denotes R₃ or R₄, and R₃ and R₄ are as defined above or a derivative thereof with 1 to 10 moles, preferably 1 to 3 moles of diphenylphosphoryl azide, trimethylsilylazide or the like, per mole of the carboxylic acid, in an organic solvent to give an acyl azide, which is in turn subjected to a rearrangement reaction under heating at 50-150°C, or alternatively by reacting a compound of formula (V) or (II) with phosgen.

25 The carbamate of formula (VI) or (VII) are prepared by reacting a compound of formula (II) or (V) with 0.1 to 10 moles, preferably 0.5 to 2 moles of phenyl chloroformate per mole of the compound in an organic solvent under ice-cooling or at a temperature up to room temperature. This reaction may be conducted in the presence of an acid binder. The acid binders include e.g. inorganic basic substances such as sodium hydride, potassium hydroxide, sodium carbonate, potassium carbonate and organic basic substances including secondary amines such as diisopropylamine and tertiary amines such as triethylamine, methylmorpholine, pyridine.

30 The organic solvents used in each of the above-described reactions include aliphatic hydrocarbon solvents such as hexane, petroleum ether and cyclohexane, aromatic hydrocarbon solvents such as benzene, toluene and xylenes, halogenated hydrocarbon solvents such as methylene chloride, chloroform, carbon tetrachloride and dichloroethane, ether solvents such as ethyl ether, isopropyl ether, tetrahydrofuran and dioxane, ketone solvents such as acetone and methyl ethyl ketone, ethyl acetate, acetonitrile and N,N-dimethylformamide.

35 The process steps for the compounds of the invention according to the reactions as described above are shown in the following scheme 1:

35

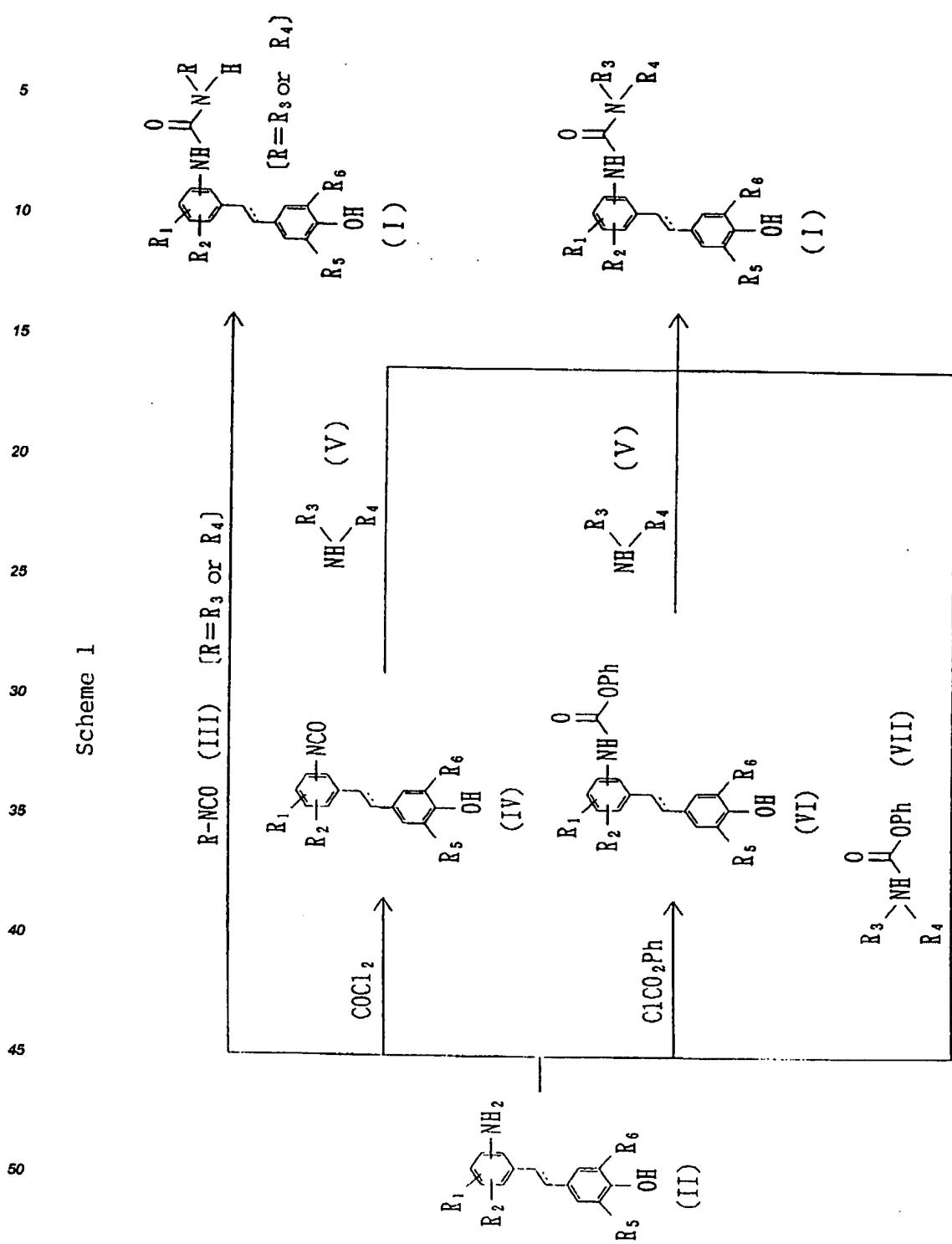
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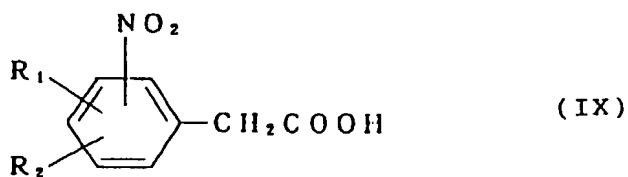
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Scheme 1



55 The compounds of formula (III) are prepared by reacting a nitrophenylacetic acid derivative of formula (IX)

5



wherein R₁ and R₂ are as defined above with a benzaldehyde derivative of formula (VIII)

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15

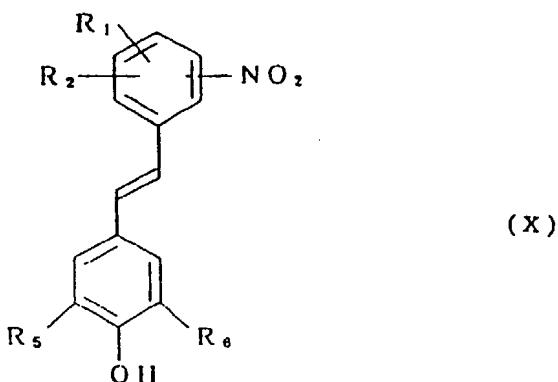


20 wherein R₅ and R₆ are as defined above while heating at 100 to 200°C in the presence of a catalytic amount of a basic material such as piperidine, to form a compound of formula (X)

25

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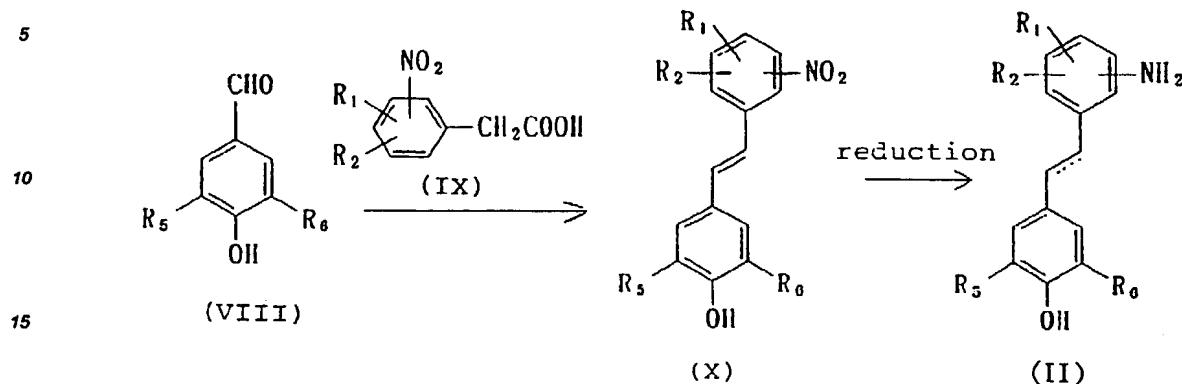
wherein R₅ and R₆ are as defined above, followed by reduction. The reaction is performed using the compound of formula (VIII) in an amount of 0.1 to 10 moles, preferably 0.5 to 2 moles per mole of the compound of formula (IX). The reduction process includes e.g. that using zinc, iron, tin, stannous chloride or the like in an acidic solution such as hydrochloric acid, acetic acid or a catalytic hydrogenation using a catalyst such as palladium carbon, platinum oxide or the like. The process steps by the reactions as described above are shown in the following scheme 2:

45

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Scheme 2



20 Pharmaceutically acceptable salts of the compounds of formula (I) may be formed in conventional way. The acid addition salts may be formed for example by reaction of the base compound of formula (I) with a pharmaceutically acceptable inorganic acid such as hydrochloric, hydrobromic, hydroiodic, sulfuric and phosphoric acids or a pharmaceutically acceptable organic acid such as oxalic, maleic, fumaric, lactic, malic, citric, tartaric, benzoic and methanesulphonic acids.

25 The compounds of formula (I) according to the present invention possess both an ACAT inhibitor activity and an antioxidative activity, especially a protective ability against an oxidative modification of LDL. By the ACAT inhibitory activity, the present compounds can inhibit an absorption of cholesterol from the intestinal tracts, reduce a plasma cholesterol level and inhibit an accumulation of cholestryl esters in the wall of blood vessels, atheroma lesion and macrophage. By the antioxidative activity, especially a protective activity against the oxidative modification of LDL, the present compounds can inhibit the formation and progression of atherosclerosis lesion and inducing its regression.

30

Thus, the compounds of the present invention are useful in the prophylaxis or treatment of hypercholesterolemia and atherosclerosis.

According to another aspect of the present invention, there is provided an ACAT inhibitor comprising the compound of formula (I) or a pharmaceutically acceptable salt thereof.

In further aspects, the present invention provides a pharmaceutical composition for the prophylaxis or treatment of hypercholesterolemia or atherosclerosis, which comprises as an active ingredient the compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier and/or excipient.

40 The compounds of the invention can usually be administered orally or parenterally in the form of a pharmaceutical preparation. The pharmaceutical preparations include tablets, capsules, troches, syrups, granules, powders, injections, suspensions and the like. It may be in bilayered or multilayered tablet with other drugs. The tablets may also be coated with a conventional coating to form, e.g., sugar-coated, enteric-coated or film-coated tablets.

45 In preparing solid preparations, additives such as lactose, refined sugar, crystalline cellulose, corn starch, calcium phosphate, sorbitol, glycine, carboxymethylcellulose, gum arabic, polyvinylpyrrolidone, hydroxypropylcellulose, polyethylene glycol, stearic acid, magnesium stearate and talc are employed.

A vegetable or synthetic wax or fat or a similar base is used in preparing the semi-solid preparations.

As additives in preparing the liquid preparations are used, for example, sodium chloride, sorbitol, glycerin, olive oil, almond oil, propylene glycol and ethyl alcohol.

The active ingredient is contained in the formulation in an amount of 0.0001-100% by weight, suitably 0.001-50% by weight in the case of formulations for oral administration and 0.0001-10% by weight in the case of formulations for injection based on the weight of the preparations.

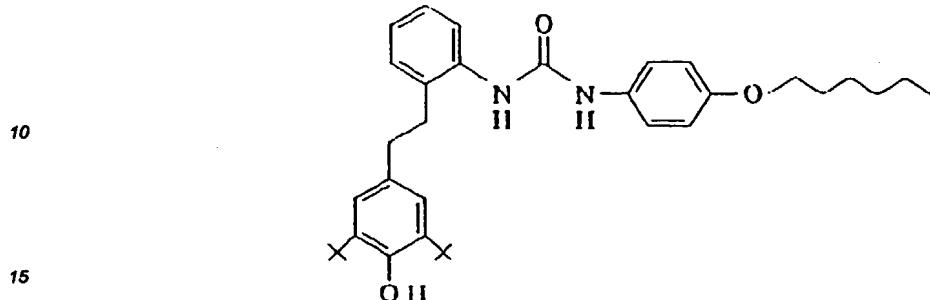
55 Route and dosage of administration for the compounds of the invention are not specifically limited and are appropriately chosen depending upon form of the formulation, age and sex of the patient, severity of the disease and other factors. Daily dosage of the active ingredient is 0.01-1000 mg. No adverse toxicological effects are indicated at any of the above dosage ranges.

The invention is further illustrated by the following examples.

Example 1

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(4-hexyloxyphenyl)urea

5



10 A solution of diphenylphosphorylazide (0.93 g, 3.4 mmol), 4-hexyloxybenzoic acid (0.68 g, 3.1 mmol) and triethylamine (0.34 g, 3.4 mmol) in toluene (10 ml) was stirred at room temperature for 3.5 hrs and heated at 20 about 90°C for 2 hrs with stirring. After allowing the mixture to cool (under 0°C), a solution of 4-(2-aminophenethyl)-2,6-di-tert-butylphenol (1.0 g, 3.1 mmol) in toluene (4 ml) was added dropwise. The solution was warmed up to room temperature and stirred overnight. After distilling off the solvent and purification of the residue by a silica gel column chromatography, recrystallization from ethyl acetate/hexane afforded N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(4-hexyloxyphenyl)urea (1.2 g, 71% yield). m.p. 174-176°C

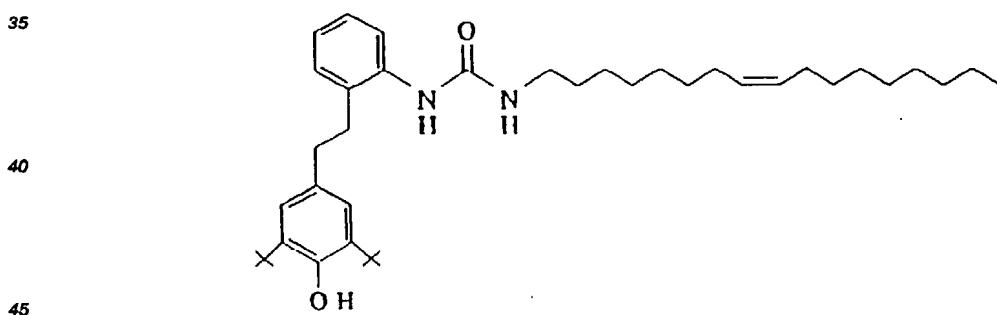
25 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.40-7.42(m, 1H), 7.14-7.26(m, 5H), 6.81(s, 2H), 6.76-6.79(m, 2H), 5.98(s, 1H), 5.39(s, 1H), 5.13(s, 1H), 3.88(t, $J=7\text{Hz}$, 2H), 2.83-2.87(m, 2H), 2.76-2.80(m, 2H), 1.70-1.77(m, 2H), 1.38(s, 18H), 1.30-1.45(m, 6H), 0.87-0.93(m, 3H)

IR (cm^{-1}) 3640, 3310, 2950, 1630, 1560, 1490, 1440, 1230

30 Example 2

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(8-heptadecenyl)urea

35



40 The title compound was prepared in a similar manner to that mentioned in Example 1, using 9-octadecenoic acid instead of 4-hexyloxybenzoic acid.

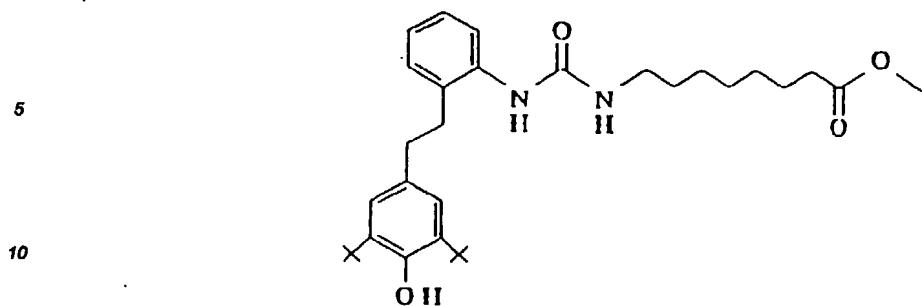
45 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.16-7.26(m, 4H), 6.78(s, 2H), 5.29-5.34(m, 2H), 5.12(s, 1H), 5.00(s, 1H), 4.19(t, $J=6\text{Hz}$, 1H), 3.11(dd, $J=14, 6\text{Hz}$, 2H), 2.77-2.87(m, 4H), 1.93-2.02(m, 4H), 1.38(s, 18H), 1.18-1.38(m, 25H)

IR (cm^{-1}) 3642, 3288, 2926, 1639, 1558, 1435, 1233, 750

Example 3

55

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(7-methoxycarbonylheptyl)urea



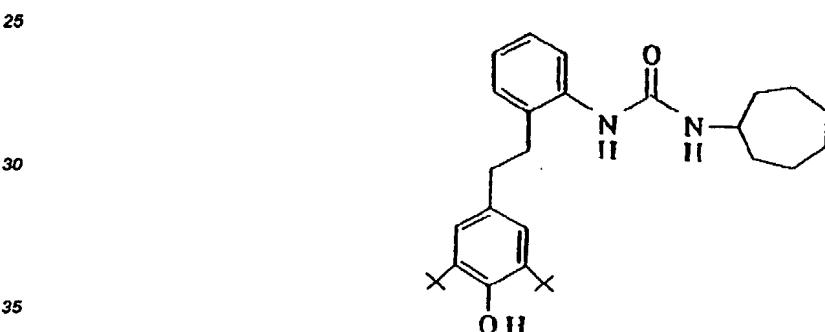
15 The title compound was prepared in a similar manner to that mentioned in Example 1, using 8-methoxy-carbonyloctanoic acid instead of 4-hexyloxybenzoic acid

1H-NMR (δ ppm, CDCl_3) 7.16-7.26(m, 4H), 6.78(s, 2H), 5.12(s, 1H), 4.98(s, 1H), 4.17(t, $J=6\text{Hz}$, 1H), 3.66(s, 3H), 3.09-3.14(m, 2H), 2.77-2.87(m, 4H), 2.28(t, $J=8\text{Hz}$, 2H), 1.53-1.61(m, 2H), 1.38(s, 18H), 1.18-1.30(m, 6H), 0.88(t, $J=7\text{Hz}$, 2H)

20 IR (cm^{-1}) 3640, 2928, 1737, 1639, 1547, 1436, 1234

25 Example 4

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-cycloheptylurea



35 The title compound was prepared in a similar manner to that mentioned in Example 1, using cycloheptanecarboxylic acid instead of 4-hexyloxybenzoic acid. m.p. 177-178°C

40 1H-NMR (δ ppm, CDCl_3) 7.17-7.26(m, 4H), 6.79(s, 2H), 5.10(s, 1H), 5.05(bs, 1H), 4.19(d, $J=8\text{Hz}$, 1H), 3.75-3.85(m, 1H), 2.80-2.88(m, 2H), 2.75-2.80(m, 2H), 1.83-1.90(m, 2H), 1.38(s, 18H), 1.21-1.58(m, 10H)

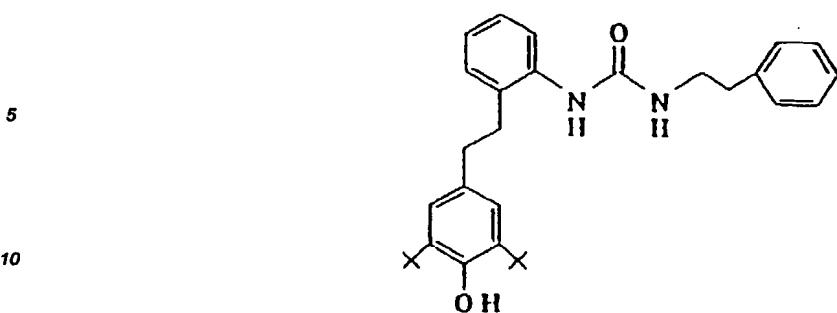
IR (cm^{-1}) 3650, 3300, 2930, 2860, 1630, 1570, 1440, 1240

45 Example 5

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-phenethylurea

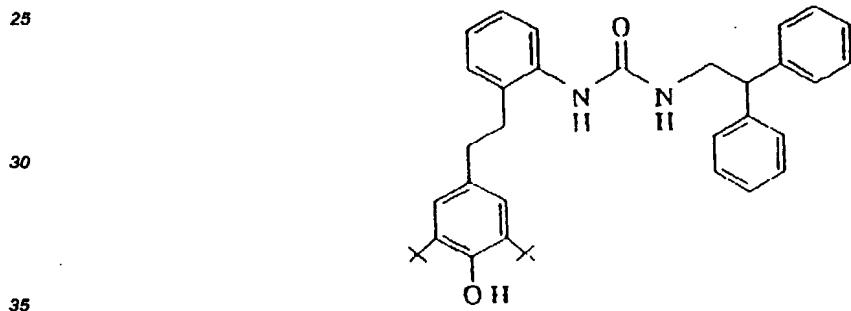
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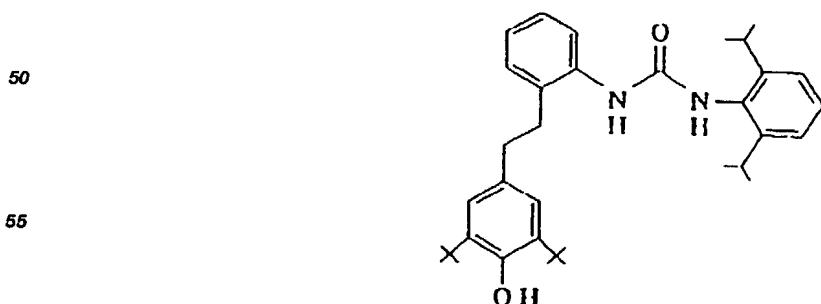
20 Example 6

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(2,2-diphenylethyl)urea



Example 7

45 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(2,6-diisopropylphenyl)urea



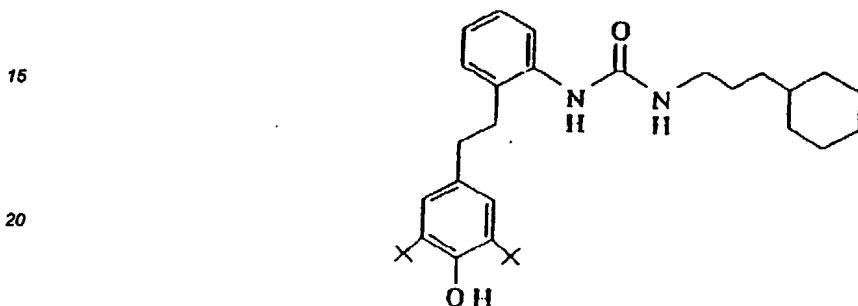
The title compound was prepared in a similar manner to that mentioned in Example 1, using 2,6-dilisopropylbenzoic acid instead of 4-hexyloxybenzoic acid. m.p. 209-210°C

1H-NMR (δ ppm, DMSO) 8.01(bs, 1H), 7.85(bs, 1H), 7.65(d, J=8Hz, 1H), 7.20-7.24(m, 1H), 7.10-7.14(m, 4H), 6.93-6.97(m, 3H), 6.62(s, 1H), 3.32-3.53(m, 1H), 3.18-3.25(m, 1H), 2.75-2.85(m, 4H), 1.37(s, 18H), 1.13(d, 5 J=7Hz, 12H)

IR (cm⁻¹) 3612, 3320, 2958, 1646, 1586, 1534, 1435, 1231, 745

Example 8

10 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(3-cyclohexylpropyl)urea



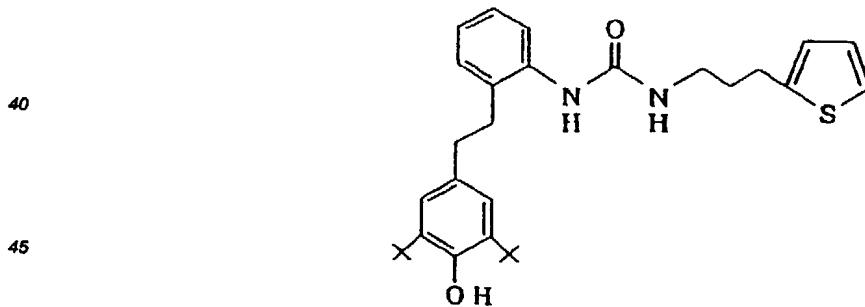
25 The title compound was prepared in a similar manner to that mentioned in Example 1, using 4-cyclohexylbutanoic acid instead of 4-hexyloxybenzoic acid. m.p. 166°C

1H-NMR (δ ppm, CDCl₃) 7.18-7.26(m, 4H), 6.78(s, 2H), 5.11(s, 1H), 5.02(s, 1H), 4.20(t, 1H), 3.10 (dt, J=6, 7Hz, 2H), 2.83-2.85(m, 2H), 2.76-2.80(m, 2H), 1.56-1.68(m, 4H), 1.38(s, 18H), 1.33-1.43(m, 2H), 1.04-1.30(m, 6H), 0.75-0.88(m, 3H)

30 IR (cm⁻¹) 3640, 3316, 2924, 1640, 1558, 1436, 1233, 749

Example 9

35 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(3-(2-thienyl)propyl)urea



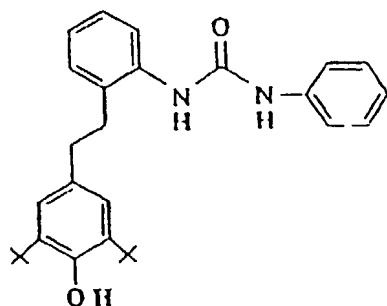
50 The title compound was prepared in a similar manner to that mentioned in Example 1, using 4-(2-thienyl)butanoic acid instead of 4-hexyloxybenzoic acid. m.p. 150°C

1H-NMR (δ ppm, CDCl₃) 7.19-7.27(m, 4H), 7.07(dd, J=4, 1Hz, 1H), 6.87(dd, J=3, 2Hz, 1H), 6.77(s, 2H), 6.71(t, J=2Hz, 1H), 5.11(s, 1H), 4.96(s, 1H), 4.21(t, 1H), 3.20(s, 2H), 2.77-2.87(m, 6H), 1.81(qui, J=7Hz, 2H), 1.37(s, 18H)

55 IR (cm⁻¹) 3638, 3286, 2918, 1630, 1570, 1434, 1233, 696

Example 10

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-phenylurea

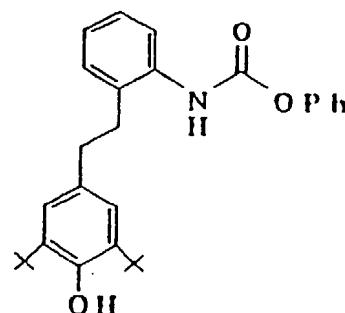


The title compound was prepared in a similar manner to that mentioned in Example 1, using benzoic acid instead of 4-hexyloxybenzoic acid, m.p. 207°C.

15 ¹H-NMR (δ ppm, CDCl₃) 7.22-7.36(m, 8H), 7.02(t, J=7Hz, 1H), 6.80(s, 2H), 6.02(s, 1H), 5.18(s, 1H), 5.15(s, 1H), 2.79-2.91(m, 4H), 1.38(s, 18H)

Example 11

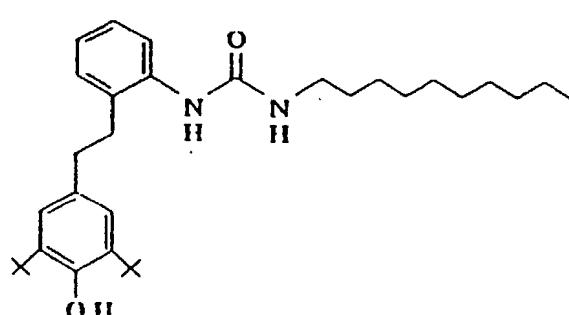
20 (1) N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]phenyl carbamate



35 To a solution of 4-(2-aminophenethyl)-2,6-di-tert-butylphenol (7.00 g, 21.5 mmol) and diisopropylamine (3.4 ml, 24 mmol) in dichloromethane (50 ml) was added dropwise a solution of phenyl chloroformate (3.60 g, 23.0 mmol) in dichloromethane (10 ml) so that the internal temperature does not exceed 0°C over a ice-cold water bath. The mixture was stirred at the same temperature for 2 hrs, washed with water, dried over MgSO_4 and concentrated. Purification of the residue by a silica gel column chromatography gave a viscous oil of N-[2-(2,6-di-tert-butyl-4-hydroxyphenethyl)benzyl]benzyl carbamate (2.12 g, 25.2% yield).

¹H-NMR (8 ppm, CDCl₃) 7.63(bs, 1H), 7.34(t, J=8Hz, 2H), 7.08-7.29(m, 6H), 6.80(s, 2H), 5.74(bs, 1H), 5.12(s, 1H), 2.8-2.8(m, 4H), 1.25(s, 1H).

(2) N-[2-(3,5-di-*t*-butyl-4-hydroxyphenethyl)phenyl]-N'-(*o*-diphenyl-



A solution of N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]phenyl carbamate (1.0 g, 2.2 mmol) and decylamine (0.38 g, 2.4 mmol) in xylene (10 ml) was heated under reflux for 2.5 hrs. After distilling off the solvent, purification of the residue by a silica gel column chromatography afforded waxy N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-decylurea (0.93 g, 85% yield).

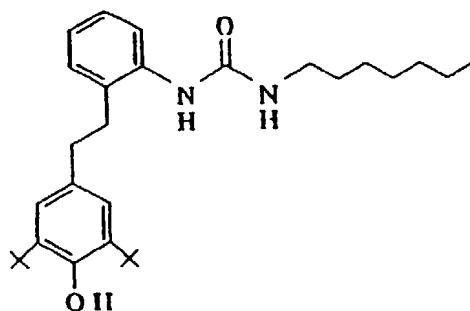
5 ¹H-NMR (δ ppm, CDCl₃) 7.17-7.26(m, 4H), 6.78(s, 2H), 5.11(s, 1H), 4.98(s, 1H), 4.17(t, J=6Hz, 1H),
3.09-3.16(m, 2H), 2.76-2.87(m, 4H), 1.50-2.50(m, 16H), 1.38(s, 18H), 0.87(t, J=7Hz, 3H)
IR (cm⁻¹) 3650, 3350, 2960, 2930, 2850, 1640, 1570

Example 12

10

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-heptylurea

15



20

25

The title compound was prepared in a similar manner to that mentioned in Example 11, using heptylamine instead of decylamine. m.p. 100°C

1H-NMR (δ ppm, CDCl₃) 7.18-7.27(m, 4H), 6.78(s, 2H), 5.11(s, 1H), 4.99(s, 1H), 4.18(bt, J=5Hz, 1H),
2.89(q, J=6Hz, 2H), 2.79-2.85(m, 4H), 1.38-1.45(m, 2H), 1.38(s, 18H), 1.15-1.30(m, 8H), 0.86(t, J=7Hz, 3H)
IR (cm⁻¹) 3650, 3320, 2970, 2940, 2870, 1640, 1570, 1440, 1240, 760

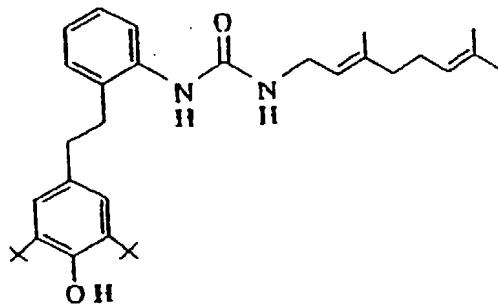
Example 13

35

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(3,7-dimethyl-2,6-octadienyl)urea

36

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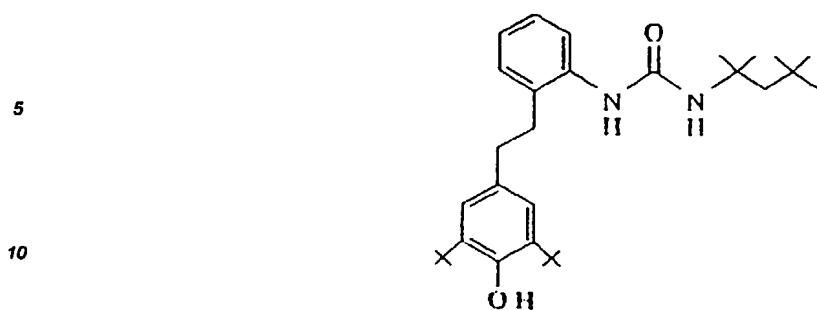
55

The title compound was prepared in a similar manner to that mentioned in Example 11, using 3,7-dimethyl-2,6-octadienylamine instead of decylamine. m.p. 87.0-87.5°C

1H-NMR (δ ppm, CDCl₃) 7.16-7.30(m, 4H), 6.78(s, 2H), 5.10(s, 1H), 5.05-5.13(m, 1H), 5.02(bs, 2H),
4.05-4.12(m, 1H), 3.75(t, J=6Hz, 2H), 2.80-2.85(m, 2H), 2.75-2.80(m, 2H), 1.95-2.08(m, 2H), 1.89-1.95(m, 2H),
1.65(s, 3H), 1.60(s, 3H), 1.57(s, 3H), 1.37(s, 18H)
IR (cm⁻¹) 3628, 3312, 2956, 1638, 1585, 1436, 1233, 752

Example 14

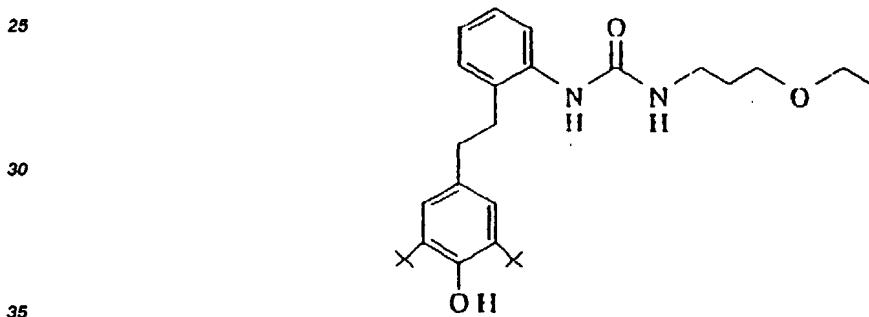
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(2,4,4-trimethyl-2-pentyl)urea



The title compound was prepared in a similar manner to that mentioned in Example 11, using 2,2,4-trimethyl-2-pentylamine instead of decylamine. m.p. 168-169°C
 1H-NMR (δ ppm, CDCl_3) 7.15-7.26(m, 4H), 6.83(s, 2H), 5.09(s, 2H), 4.18(s, 1H), 2.71-2.87(m, 4H), 1.64(s, 2H), 1.39(s, 18H), 1.34(s, 6H), 0.90(s, 9H)
 IR (cm^{-1}) 3640, 3334, 2956, 1645, 1556, 1437, 1365, 1226

20 Example 15

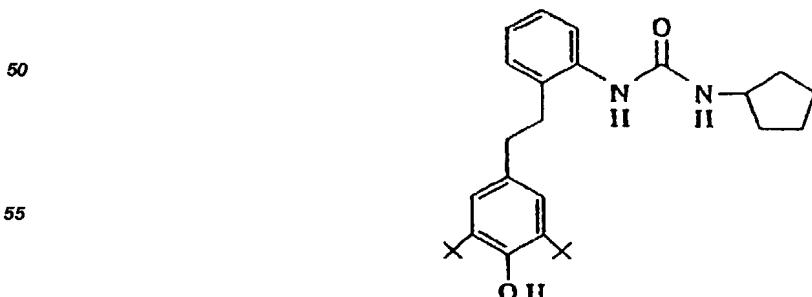
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(3-ethoxypropyl)urea



The title compound was prepared in a similar manner to that mentioned in Example 11, using 3-ethoxypropylamine instead of decylamine. m.p. 136-137°C
 1H-NMR (δ ppm, CDCl_3) 7.16-7.27(m, 4H), 6.79(s, 2H), 5.10(s, 1H), 5.06(s, 1H), 4.78(t, $J=5\text{Hz}$, 1H), 3.40(t, $J=6\text{Hz}$, 2H), 3.32(dd, $J=14, 7\text{Hz}$, 2H), 3.28(q, $J=6\text{Hz}$, 2H), 2.84-2.88(m, 2H), 2.77-2.80(m, 2H), 1.67-1.73(m, 2H), 1.38(s, 18H), 0.99(t, $J=7\text{Hz}$, 3H)
 IR (cm^{-1}) 3600, 3346, 2952, 1638, 1563, 1436, 1288, 1238, 1108, 753

40 Example 16

45 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-cyclopentylurea



The title compound was prepared in a similar manner to that mentioned in Example 11, using cyclopentylamine instead of decylamine. m.p. 186-187°C

⁵ ¹H-NMR (δ ppm, CDCl₃) 7.15-7.28(m, 4H), 6.79(s, 2H), 5.11(s, 1H), 5.08(s, 1H), 4.17(d, J=7Hz, 1H), 4.01-4.10(m, 1H), 2.76-2.87(m, 4H), 1.89-1.96(m, 2H), 1.50-1.61(m, 4H), 1.39(s, 18H), 1.22-1.29(m, 2H)
IR (cm⁻¹) 3650, 3350, 2950, 1640, 1580, 1560, 1440, 1240

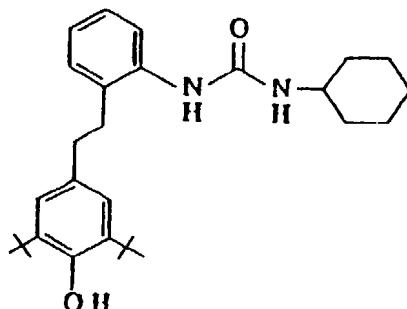
Example 17

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-cyclohexylurea

¹⁰

¹⁵

²⁰



The title compound was prepared in a similar manner to that mentioned in Example 11, using cyclohexylamine instead of decylamine. m.p. 198-200°C

²⁵ ¹H-NMR (δ ppm, CDCl₃) 7.16-7.25(m, 4H), 6.78(s, 2H), 5.14(s, 1H), 4.99(s, 1H), 4.09(d, J=5Hz, 1H), 3.59-3.62(m, 1H), 2.83(d, J=6Hz, 2H), 2.79(d, J=6Hz, 2H), 1.95-1.99(m, 2H), 1.53-1.64(m, 4H), 1.38(s, 18H), 1.26-1.30(m, 2H), 0.96-0.99(m, 2H)
IR (cm⁻¹) 3290, 2930, 1630, 1561, 1232

³⁰

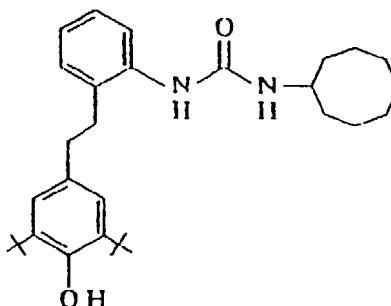
Example 18

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-cyclooctylurea

³⁵

⁴⁰

⁴⁵

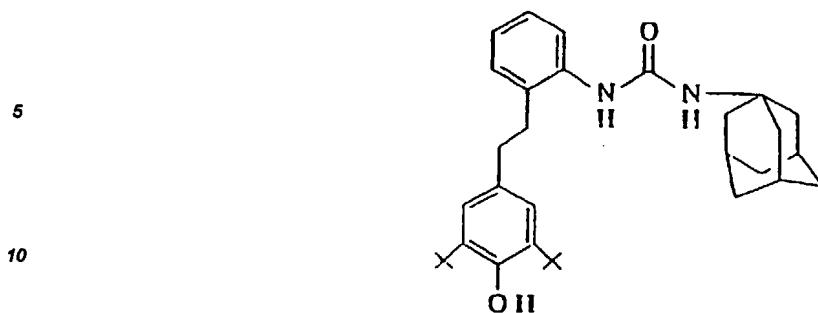


The title compound was prepared in a similar manner to that mentioned in Example 11, using cyclooctylamine instead of decylamine. m.p. 174-176°C

⁵⁰ ¹H-NMR (δ ppm, CDCl₃) 7.17-7.24(m, 4H), 6.79(s, 2H), 5.10(s, 1H), 5.05(s, 1H), 4.19(d, J=5Hz, 1H), 3.68-3.98(m, 1H), 2.83(d, J=6Hz, 2H), 2.79(d, J=6Hz, 2H), 1.74-1.81(m, 2H), 1.42-1.58(m, 12H), 1.38(s, 18H)
IR (cm⁻¹) 3308, 2922, 1630, 1554, 1435, 1233

Example 19

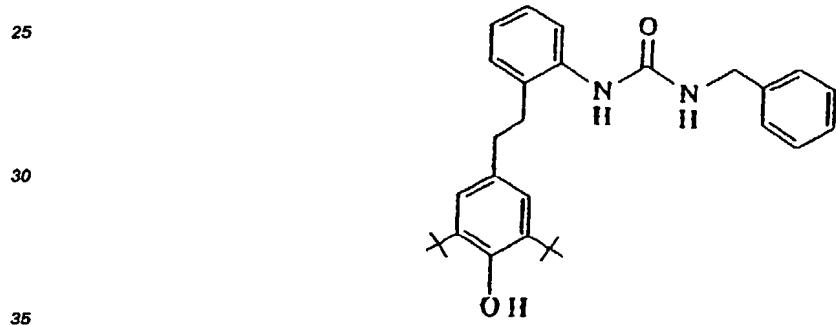
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-adamantylurea



The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-adamantanamine instead of decylamine. m.p. 197-199°C
 1H-NMR (δ ppm, CDCl_3) 7.14-7.29(m, 4H), 6.83(s, 2H), 5.11(s, 1H), 5.10(s, 1H), 4.06(s, 1H), 2.79-2.85(m, 4H), 1.91-2.05(m, 9H), 1.60-1.70(m, 6H), 1.39(s, 18H)
 IR (cm^{-1}) 3350, 2900, 2850, 1640, 1550, 1440, 1300, 1240

25 Example 20

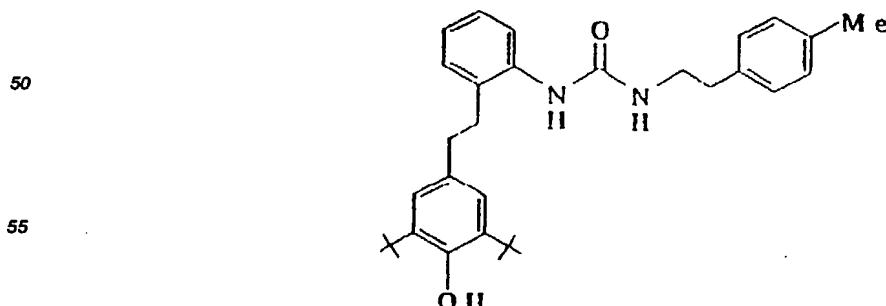
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-benzylurea



The title compound was prepared in a similar manner to that mentioned in Example 11, using benzylamine instead of decylamine. m.p. 181-183°C
 1H-NMR (δ ppm, CDCl_3) 7.15-7.30(m, 9H), 6.77(s, 2H), 5.13(s, 1H), 5.08(s, 1H), 4.54(t, $J=6\text{Hz}$, 1H), 4.33(d, $J=6\text{Hz}$, 2H), 2.82(d, $J=6\text{Hz}$, 2H), 2.78(d, $J=6\text{Hz}$, 2H), 1.35(s, 18H)
 IR (cm^{-1}) 3294, 2956, 1629, 1579, 1435, 1233, 741

Example 21

45 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(4-methylphenethyl)urea



The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-methylphenethylamine instead of decylamine.

m.p. 170-172°C

⁵ ¹H-NMR (δ ppm, CDCl₃) 7.12-7.23(m, 4H), 7.04(d, J=8Hz, 2H), 6.98(d, J=8Hz, 2H), 6.76(s, 2H), 5.09(s, 1H), 4.96(s, 1H), 4.22(t, J=6Hz, 1H), 3.36(q, J=6Hz, 2H), 2.80(d, J=6Hz, 2H), 2.69(t, J=6Hz, 2H), 2.68(d, J=6Hz, 2H), 2.29(s, 3H), 1.36(s, 18H)

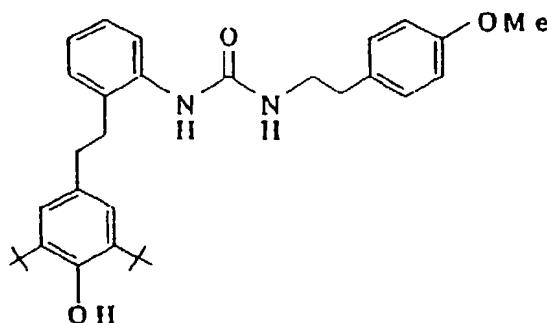
IR (cm⁻¹) 3342, 2950, 1643, 1563, 1435

Example 22

¹⁰

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(4-methoxyphenethyl)urea

¹⁵



²⁰

²⁵

The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-methoxyphenethylamine instead of decylamine.

m.p. 148-149°C

³⁰ ¹H-NMR (δ ppm, CDCl₃) 7.10-7.24(m, 4H), 7.00(d, J=9Hz, 2H), 6.77(d, J=9Hz, 2H), 6.76(s, 2H), 5.09(s, 1H), 4.95(s, 1H), 4.20(t, J=6Hz, 1H), 3.76(s, 3H), 3.33(q, J=6Hz, 2H), 2.80(d, J=6Hz, 2H), 2.77(d, J=6Hz, 2H), 2.67(t, J=6Hz, 2H), 1.36(s, 18H)

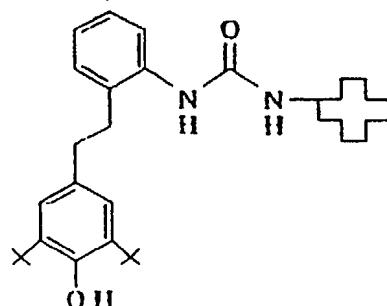
IR (cm⁻¹) 3420, 2960, 1641, 1561, 1525, 1249

Example 23

³⁵

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-cyclododecylurea

⁴⁰



⁴⁵

⁵⁰

The title compound was prepared in a similar manner to that mentioned in Example 11, using cyclododecylamine instead of decylamine.

¹H-NMR (δ ppm, CDCl₃) 7.06-7.29(m, 4H), 6.80(s, 2H), 5.10(s, 2H), 4.05(d, J=9Hz, 1H), 3.89(s, 1H), 2.76-2.87(m, 4H), 1.38(s, 18H), 1.20-1.30(m, 22H)

IR (cm⁻¹) 3650, 3340, 2950, 2920, 1640, 1560, 1440, 1240

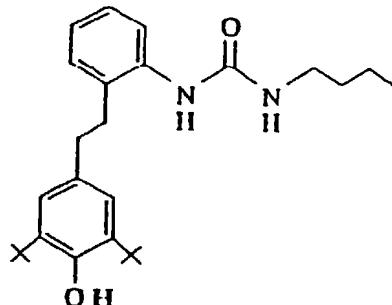
Example 24

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-butylurea

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15



The title compound was prepared in a similar manner to that mentioned in Example 11, using butylamine instead of decylamine. m.p. 133-134°C

20 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.16-7.26(m, 4H), 6.78(s, 2H), 5.12(s, 1H), 4.97(s, 1H), 4.16(t, $J=6\text{Hz}$, 1H), 3.11-3.16(m, 2H), 2.77-2.87(m, 4H), 1.38(s, 18H), 1.21-1.34(m, 4H), 0.87(t, $J=7\text{Hz}$, 3H)
 IR (cm^{-1}) 3450, 3320, 2960, 1640, 1570, 1460, 1440, 1250, 1230

Example 25

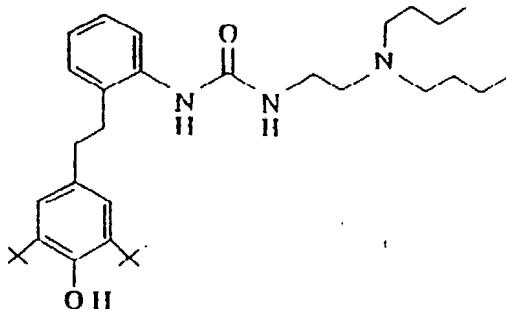
25

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[2-(N,N-dibutylamino)ethyl]urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using N,N-dibutylethylenediamine instead of decylamine.

45 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.18-7.26(m, 4H), 6.80(s, 2H), 5.18(s, 1H), 5.10(s, 1H), 5.02(bs, 1H), 3.17-3.21(m, 2H), 2.76-2.87(m, 4H), 2.40(t, $J=6\text{Hz}$, 2H), 2.24(t, $J=7\text{Hz}$, 4H), 1.38(s, 18H), 1.04-1.26(m, 8H), 0.82(t, $J=7\text{Hz}$, 6H)
 IR (cm^{-1}) 3650, 3360, 2960, 2880, 1640, 1560, 1440, 1240

Further, the hydrochloride of the title compound was prepared in the following manner.

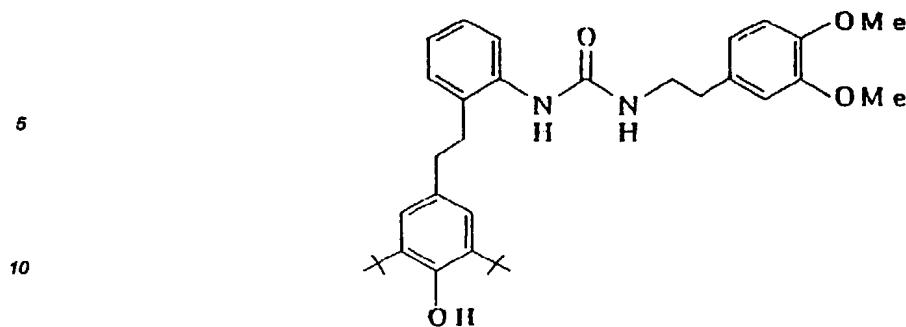
Conc. hydrochloric acid (0.17 ml) was added to a solution of the title compound (0.95 g) in ethanol (12 ml). Distilling off the solvent afforded a waxy hydrochloride of the title compound (1.05 g).

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Example 26

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(3,4-dimethoxyphenethyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 3,4-dimethoxyphenethylamine instead of decylamine. m.p. 158-160°C

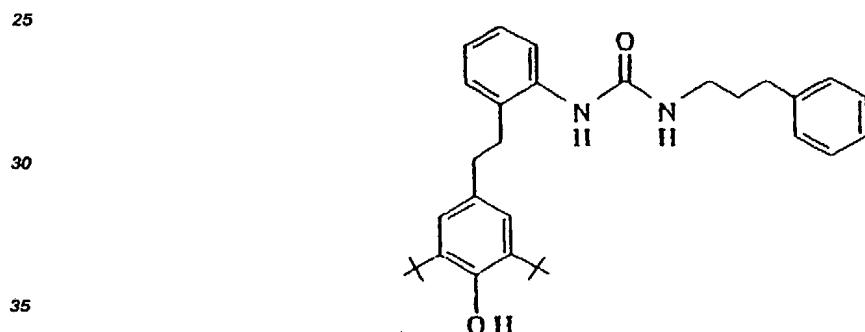
1H-NMR (δ ppm, CDCl_3) 7.10-7.24(m, 4H), 6.76(s, 2H), 6.70-6.75(m, 1H), 6.60-6.65(m, 2H), 5.10(s, 1H), 5.00(s, 1H), 4.27(t, $J=6\text{Hz}$, 1H), 3.83(s, 3H), 3.81(s, 3H), 3.35-3.40(dt, $J=6, 7\text{Hz}$, 2H), 2.72-2.84(m, 4H), 2.68(t, $J=7\text{Hz}$, 2H), 1.36(s, 18H)

IR (cm^{-1}) 3628, 3318, 1632, 1562, 1518, 1264, 1234

20

Example 27

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(3-phenylpropyl)urea



The title compound was prepared in a similar manner to that mentioned in Example 11, using 3-phenylpropylamine instead of decylamine. m.p. 161-162°C

1H-NMR (δ ppm, CDCl_3) 7.13-7.25(m, 7H), 7.10(d, $J=8\text{Hz}$, 2H), 6.77(s, 2H), 5.10(s, 1H), 4.98(s, 1H), 4.20(t, $J=7\text{Hz}$, 1H), 3.17(q, $J=7\text{Hz}$, 2H), 2.83(d, $J=6\text{Hz}$, 2H), 2.79(d, $J=6\text{Hz}$, 2H), 2.56(t, $J=7\text{Hz}$, 2H), 1.74(qui, $J=7\text{Hz}$, 2H), 1.36(s, 18H)

IR (cm^{-1}) 3628, 3328, 2952, 1637, 1562, 1435, 1234, 748, 697

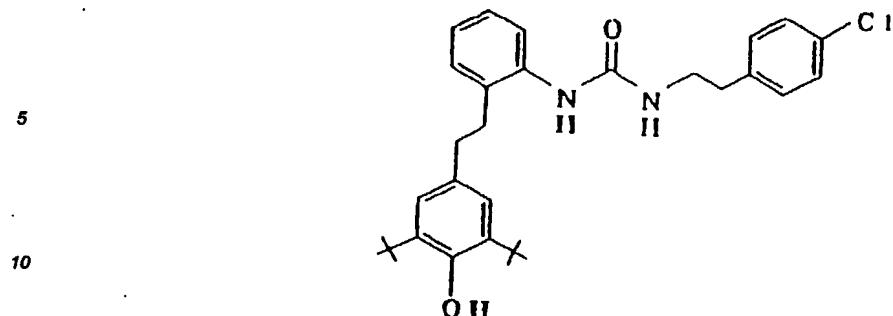
45

Example 28

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(4-chlorophenethyl)urea

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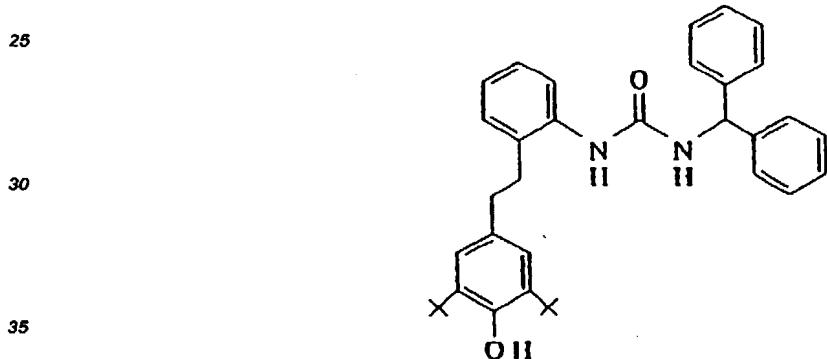


The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-chlorophenethylamine instead of decylamine. m.p. 173-174°C

¹H-NMR (δ ppm, CDCl₃) 7.09-7.20(m, 6H), 7.02(d, 2H), 6.75(s, 2H), 5.10(s, 1H), 4.91(s, 1H), 4.16(t, J=6Hz, 1H), 3.35(q, J=6Hz, 2H), 2.78(q, J=5Hz, 4H), 2.70(t, J=7Hz, 2H), 1.35(s, 18H)
 IR (cm⁻¹) 3626, 3322, 2950, 1638, 1561, 1493, 1436, 1234

20 Example 29

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-diphenylmethylurea



The title compound was prepared in a similar manner to that mentioned in Example 11, using benzhydrylamine instead of decylamine. m.p. 187.4°C

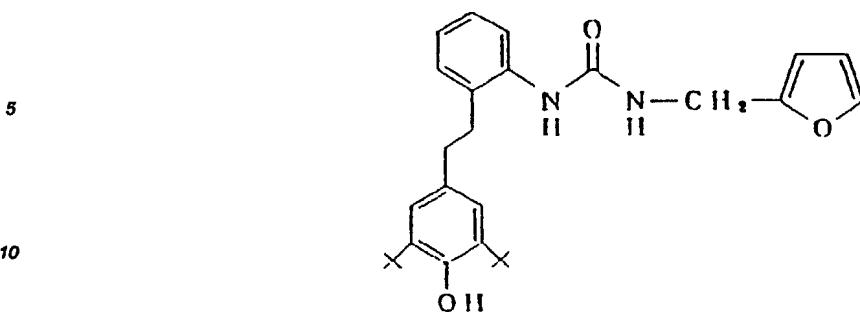
40 ¹H-NMR (δ ppm, CDCl₃) 7.14-7.33(m, 14H), 6.75(s, 2H), 6.10(d, J=8Hz, 1H), 5.17(s, 1H), 5.08(s, 1H), 4.86(d, J=8Hz, 1H), 2.73-2.81(m, 4H), 1.35(s, 18H)
 IR (cm⁻¹) 2980, 1640, 1560, 1500, 1460, 1440, 1240, 740, 700

45 Example 30

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[(2-furyl)methyl]urea

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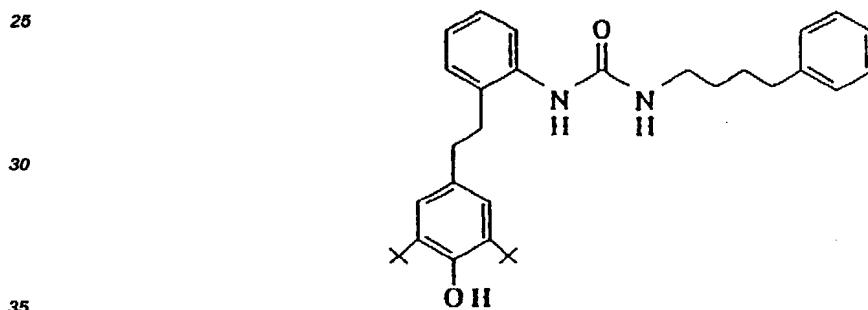
55



The title compound was prepared in a similar manner to that mentioned in Example 11, using 2-amino-
15 methylfuran instead of decylamine. m.p. 169.7°C
¹H-NMR (δ ppm, CDCl₃) 7.15-7.28(m, 5H), 6.76(s, 2H), 6.26-6.27(m, 1H), 6.14-6.15(m, 1H), 5.10(s, 1H),
4.99(s, 1H), 4.45(t, J=6Hz, 1H), 4.32(d, J=6Hz, 2H), 2.76-2.86(m, 4H), 1.36(s, 18H)
IR (cm⁻¹) 3320, 2950, 1640, 1590, 1570, 1460, 1440, 1240, 730

20 Example 31

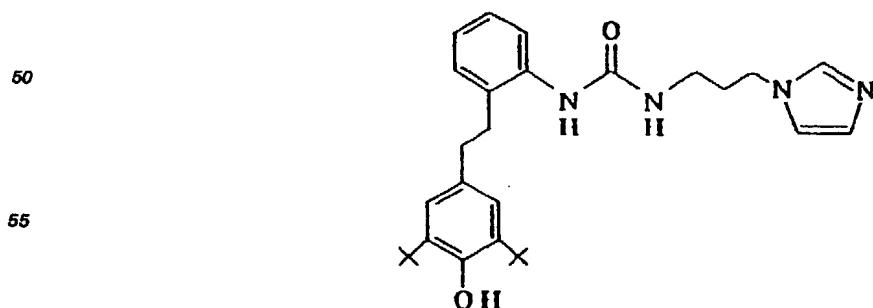
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N-(4-phenylbutyl)urea



The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-phenyl-
butylamine instead of decylamine. m.p. 157.0°C
¹H-NMR (δ ppm, CDCl₃) 7.11-7.27(m, 9H), 6.77(s, 2H), 5.10(s, 1H), 4.95(s, 1H), 4.15(t, 1H), 3.12-3.17(m,
40 2H), 2.74-2.86(m, 4H), 2.58(t, J=8Hz, 2H), 1.39-1.61(m, 4H), 1.37(s, 18H)
IR (cm⁻¹) 3300, 2950, 2860, 1620, 1600, 1580, 1440, 1250, 1240

Example 32

45 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[3-(1-imidazolyl)propyl]urea



The title compound was prepared in a similar manner to that mentioned in Example 11, using N-(3-aminopropyl)imidazole instead of decylamine.

m.p. 163.5°C

5 ¹H-NMR (δ ppm, CDCl₃) 7.39(s, 1H), 7.20-7.29(m, 4H), 7.01(s, 1H), 6.85-6.86(m, 1H), 6.77(s, 2H), 5.15(s, 1H), 4.97(s, 1H), 4.25(t, J=6Hz, 1H), 3.92(t, J=7Hz, 2H), 3.13(dt, J=8, 7Hz, 2H), 2.77-2.86(m, 4H), 1.88-1.95(m, 2H), 1.37(s, 18H)

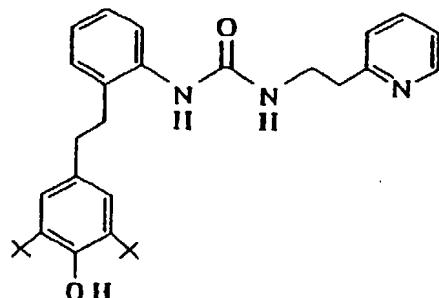
IR (cm⁻¹) 3360, 3320, 2960, 1640, 1570, 1520, 1440, 1240

Example 33

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N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N-[2-(2-pyridyl)ethyl]urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 2-(2-aminooethyl)pyridine instead of decylamine.

m.p. 179.7°C

29

¹H-NMR (δ ppm, CDCl₃) 8.32(d, J=4Hz, 1H), 7.52-7.56(m, 1H), 7.06-7.27(m, 6H), 6.77(s, 2H), 5.21(t, J=6Hz, 1H), 5.11(s, 1H), 5.10(s, 1H), 3.56(q, J=6Hz, 2H), 2.93(t, J=6Hz, 2H), 2.67-2.83(m, 4H), 1.37(s, 18H)

30

IR (cm⁻¹) 3350, 2960, 1650, 1590, 1570, 1440, 760

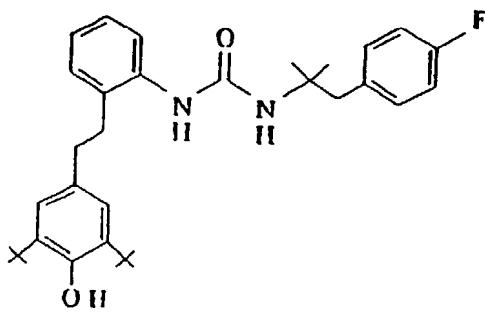
Example 34

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N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-(4-fluorophenyl)-2-methyl-2-propyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-fluoro- α , α -dimethylphenethylamine instead of decylamine.

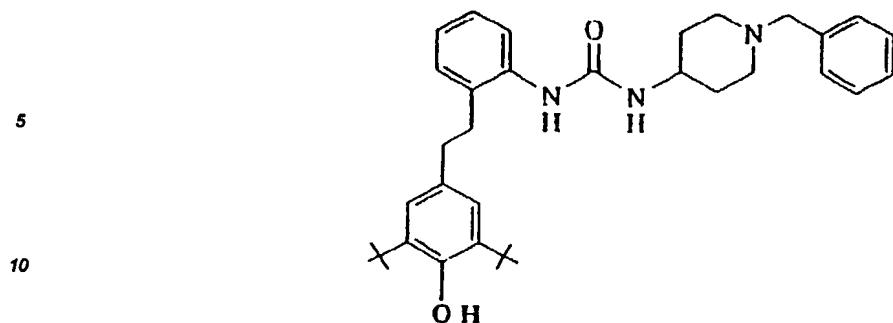
m.p. 150.6°C

55 ¹H-NMR (δ ppm, CDCl₃) 6.84-7.28(m, 8H), 6.80(s, 2H), 5.10(s, 1H), 5.09(s, 1H), 3.95(s, 1H), 2.95(s, 2H), 2.72-2.82(m, 4H), 1.37(s, 18H), 1.25(s, 6H)

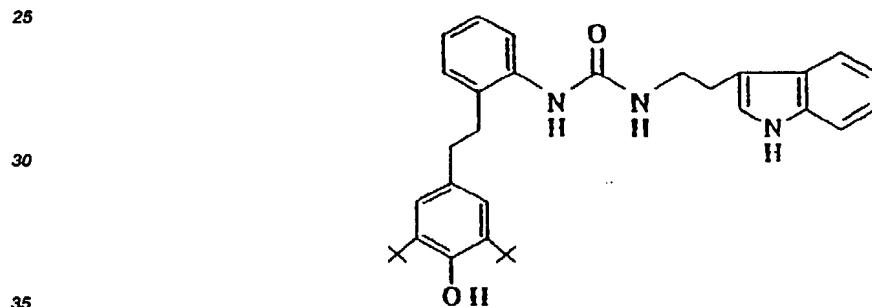
IR (cm⁻¹) 3350, 2960, 1640, 1560, 1510, 1440, 1240

Example 35

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-benzyl-4-piperidyl)urea



N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(2-(3-indolyl)ethyl)urea



The title compound was prepared in a similar manner to that mentioned in Example 11, using 3-(2-aminoethyl)indole instead of decylamine.

m.p. 193-194°C

40

1H-NMR (δ ppm, CDCl_3) 7.92(s, 1H), 7.54(d, $J=8\text{Hz}$, 1H), 7.33(d, $J=8\text{Hz}$, 1H), 7.05-7.26(m, 6H), 6.90(d, $J=2\text{Hz}$, 1H), 6.77(s, 2H), 5.10(s, 1H), 5.00(s, 1H), 4.32(t, $J=6\text{Hz}$, 1H), 3.47(dt, $J=6, 7\text{Hz}$, 2H), 2.90(t, $J=7\text{Hz}$, 2H), 2.73-2.81(m, 4H), 1.35(s, 18H)

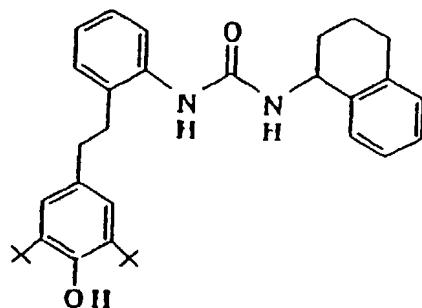
IR (cm^{-1}) 3430, 3340, 2880, 1640, 1560, 1440, 1240, 750

45 Example 37

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1,2,3,4-tetrahydro-1-naphthyl)urea

50

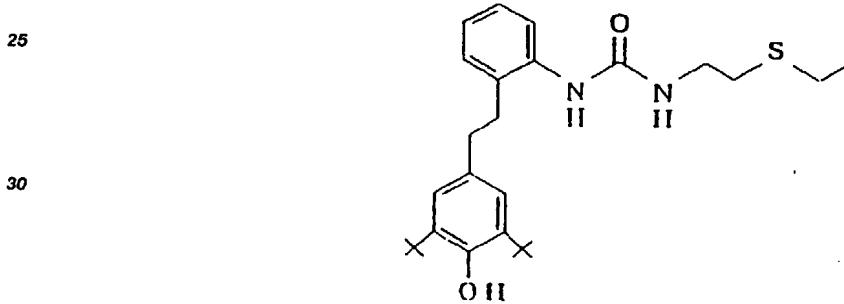
55



15 The title compound was prepared in a similar manner to that mentioned in Example 11, using 1,2,3,4-tetrahydro-1-naphthylamine instead of decylamine. m.p. 168-169°C
¹H-NMR (δ ppm, CDCl₃) 7.01-7.27(m, 8H), 6.77(s, 2H), 5.08(s, 1H), 5.01-5.06(m, 2H), 4.42(d, J=8Hz, 1H), 2.65-2.90(m, 6H), 1.50-2.10(m, 4H), 1.35(s, 18H)
IR (cm⁻¹) 3650, 3350, 2960, 1640, 1560, 1440, 1240

20 Example 38

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(2-ethylthioethyl)urea



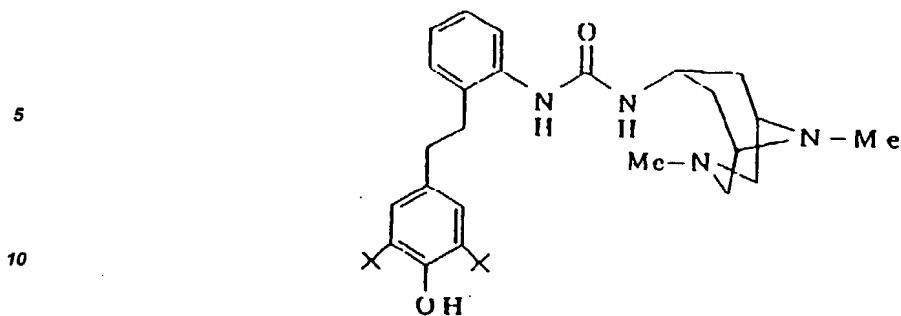
35 The title compound was prepared in a similar manner to that mentioned in Example 11, using 2-ethylthioethylamine instead of decylamine.
m.p. 131-132°C
¹H-NMR (δ ppm, CDCl₃) 7.19-7.28(m, 4H), 6.78(s, 2H), 5.12(s, 1H), 5.03(s, 1H), 4.63(t, J=6Hz, 1H), 3.33(dt, J=6, 7Hz, 2H), 2.80-2.85(m, 4H), 2.60(t, J=7Hz, 2H), 2.48(q, J=7Hz, 2H), 1.38(s, 18H), 1.20(t, J=7Hz, 3H)
IR (cm⁻¹) 3570, 3320, 2950, 2920, 1640, 1570, 1440, 1250, 1240

40 Example 39

45 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(3,9-dimethyl-3,9-diazabicyclo[3.3.1]-7-nonyl)urea

50

55



The title compound was prepared in a similar manner to that mentioned in Example 11, using 7-amino-
15 3,9-dimethyl-3,9-diazabicyclo[3.3.1]nonane instead of decylamine.

¹H-NMR (δ ppm, CDCl₃) 8.55(d, J=10Hz, 1H), 7.14-7.27(m, 4H), 6.85(s, 2H), 5.14(s, 1H), 5.09(s, 1H),
4.10-4.26(m, 1H), 2.87-2.90(m, 2H), 2.77-2.80(m, 2H), 2.70(bs, 2H), 2.41(s, 3H), 2.19-2.38(m, 7H), 1.39(s,
18H), 1.23-1.37(m, 4H)

IR(cm⁻¹) 3638, 2926, 1651, 1509, 1435, 1377, 733

20

Example 40

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-benzyl-N'-heptylurea

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30

35

The title compound was prepared in a similar manner to that mentioned in Example 11, using N-heptyl-
benzylamine instead of decylamine.

¹H-NMR (δ ppm, CDCl₃) 7.7-7.75(m, 1H), 6.9-7.3(m, 8H), 6.78(s, 2H), 5.96(s, 1H), 5.06(s, 1H), 4.49(s,
2H), 3.30(t, J=8Hz, 2H), 2.65-2.69(m, 2H), 2.51-2.54(m, 2H), 1.59-1.63(m, 2H), 1.38(s, 18H), 1.22-1.28(m, 8H),
0.86(t, J=7Hz, 3H)

IR (cm⁻¹) 3640, 2960, 2940, 2870, 1660, 1530, 1460, 1440, 1240, 760

45

Example 41

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-heptyl-N'-methylurea

50

55

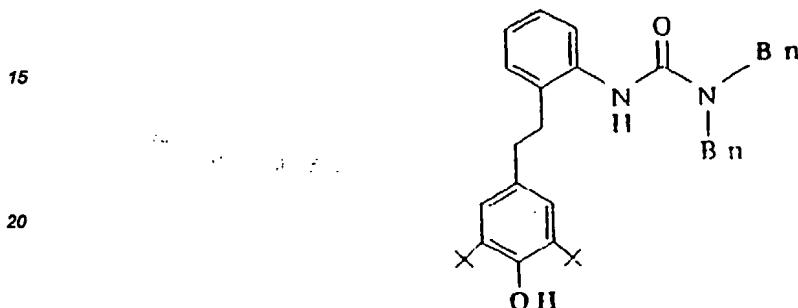
The title compound was prepared in a similar manner to that mentioned in Example 11, using N-methyl-heptylamine instead of decylamine.

¹H-NMR (δ ppm, CDCl₃) 7.36(d, J=8Hz, 1H), 7.18-7.22(m, 2H), 7.07-2.10(m, 1H), 6.81(s, 2H), 5.66(s, 1H), 5.08(s, 1H), 3.23(t, J=8Hz, 2H), 2.82(s, 4H), 2.71(s, 3H), 1.45-1.55(s, 2H), 1.36(s, 18H), 1.20-1.30(m, 8H), 0.86(t, J=7Hz, 3H)

IR (cm⁻¹) 2880, 2870, 2820, 1660, 1520, 1490, 1450, 1440, 1250, 760

Example 42

¹⁰ N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N',N'-dibenzylurea



25 The title compound was prepared in a similar manner to that mentioned in Example 11, using N,N-dibenzylamine instead of decylamine.

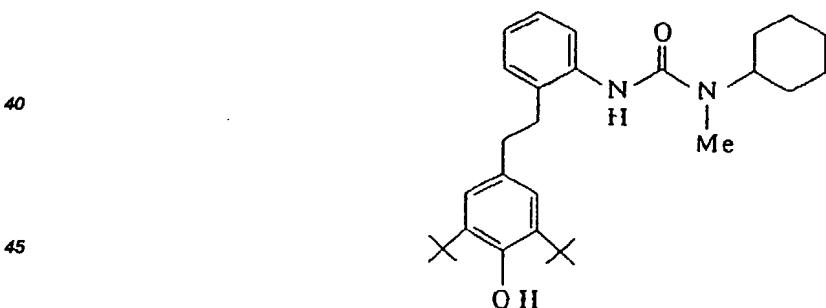
¹H-NMR (δ ppm, CDCl₃) 7.69(d, J=8Hz, 1H), 7.15-7.29(m, 10H), 7.00(m, 1H), 6.90(t, J=8Hz, 1H), 6.80(d, J=8Hz, 1H), 6.74(s, 2H), 6.01(bs, 1H), 5.05(s, 1H), 4.54(s, 4H), 2.59(t, J=8Hz, 2H), 2.38(t, J=8Hz, 2H), 1.37(s, 18H)

30 IR (cm⁻¹) 3628, 3280, 2958, 1710, 1645, 1594, 1498, 1475, 1362, 1231, 754, 696

Example 43

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-cyclohexyl-N'-methylurea

35



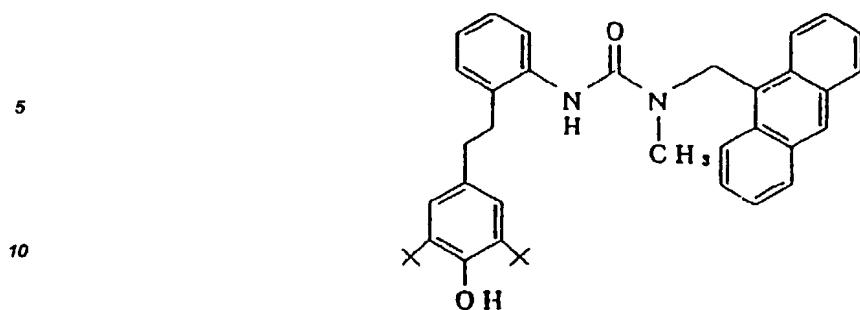
50 The title compound was prepared in a similar manner to that mentioned in Example 11, using N-methyl-cyclohexylamine instead of decylamine. Amorphous powders.

¹H-NMR (δ ppm, CDCl₃) 7.65(d, J=7Hz, 1H), 7.15-7.21(m, 2H), 7.06(t, J=7Hz, 1H), 6.81(s, 2H), 5.68(bs, 1H), 5.08(s, 1H), 4.13(m, 1H), 2.82(s, 4H), 2.54(s, 3H), 1.75-1.81(m, 2H), 1.60-1.75(m, 3H), 1.25-1.40(m, 23H)

IR (cm⁻¹) 3638, 3426, 2930, 1639, 1520, 1484, 1450, 1314, 1249, 1166, 1121, 751

55 Example 44

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N-(9-anthryl)methyl-N'-methylurea



15 The title compound was prepared in a similar manner to that mentioned in Example 11, using 9-(methylaminomethyl)anthracene instead of decylamine.

m.p. 205-206°C

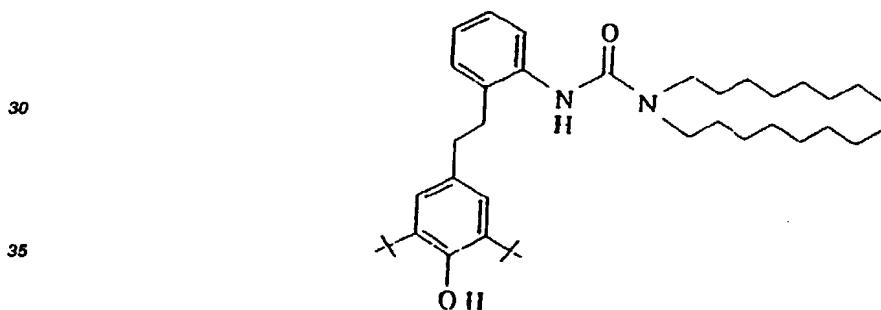
18 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 8.47(s, 1H), 8.37(d, $J=9\text{Hz}$, 2H), 8.02-8.04(m, 2H), 7.70(d, $J=8\text{Hz}$, 1H), 7.43-7.57(m, 4H), 7.15-7.31(m, 3H), 6.67(s, 2H), 5.67(s, 1H), 5.59(s, 2H), 4.94(s, 1H), 2.76-2.86(m, 4H), 2.34(s, 3H), 1.19(s, 18H)

20 $\text{IR (cm}^{-1}\text{)} 3420, 2950, 1640, 1520, 1490, 1450, 1440, 1250, 740$

Example 45

25 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N',N'-dioctylurea

25



40 The title compound was prepared in a similar manner to that mentioned in Example 11, using N,N-dioctylamine instead of decylamine. m.p. 55-60°C

43 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.73(dd, $J=8, 1\text{Hz}$, 1H), 7.13-7.25(m, 2H), 7.00-7.05(m, 1H), 6.85(s, 2H), 5.94(s, 1H), 5.07(s, 1H), 3.18(t, $J=8\text{Hz}$, 4H), 2.81(s, 4H), 1.51-1.61(m, 4H), 1.39(s, 18H), 1.20-1.34(m, 20H), 0.87(t, $J=7\text{Hz}$, 6H)

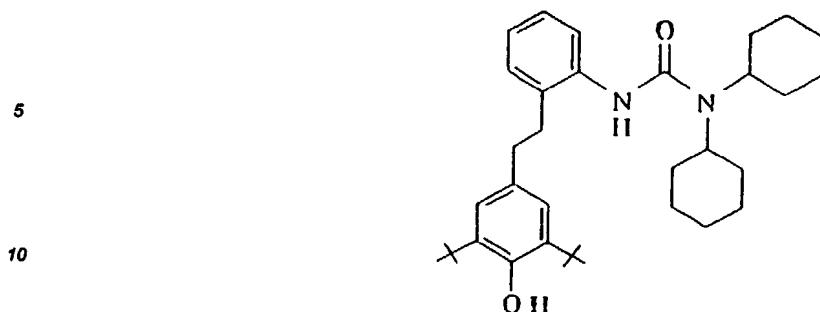
45 $\text{IR (cm}^{-1}\text{)} 3646, 3420, 3322, 1626, 1511$

Example 46

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N',N'-dicyclohexylurea

50

55



15 The title compound was prepared in a similar manner to that mentioned in Example 11, using N,N-dicyclohexylamine instead of decylamine.

m.p. 149-152°C

16 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.73(dd, $J=8, 1\text{Hz}$, 1H), 7.15-7.20(m, 1H), 7.13(dd, $J=7, 2\text{Hz}$, 1H), 7.00-7.05(m, 1H); 6.94(s, 2H), 6.15(s, 1H), 5.06(s, 1H), 3.42-3.52(m, 2H), 2.84(s, 4H), 1.55-1.83(m, 14H), 1.41(s, 18H), 1.22-1.34(m, 4H), 0.98-1.13(m, 2H)

20 IR (cm^{-1}) 3474, 3400, 1644, 1588, 1517

Example 47

N-[2-(3,5-diisopropyl-4-hydroxyphenethyl)phenyl]-N'-heptylurea

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30

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40 A solution of diphenylphosphoryl azide (0.88 g, 3.2 mmol), octanoic acid (0.42 g, 2.9 mmol) and triethylamine (0.32 g, 3.2 mmol) in toluene (10 ml) was stirred at room temperature for 1.5 hrs and further stirred at about 90°C for 2 hrs. After allowing the mixture to cool, a solution of 4-(2-aminophenethyl)-2,6-diisopropylphenol (0.85 g, 2.9 mmol) in toluene (2 ml) was added dropwise under ice-cooling while stirring. The reaction solution was returned slowly to room temperature and stirred overnight. The solvent was distilled off, the residue was purified by a silica gel column chromatography and recrystallized from ethyl acetate/hexane to give crystals of the title compound (0.99 g, 76%). m.p. 150-151°C

45 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.16-7.26(m, 4H), 6.69(s, 2H), 5.14(s, 1H), 4.73(s, 1H), 4.18(t, $J=6\text{Hz}$, 1H), 3.01-3.15(m, 4H), 2.71-2.89(m, 4H), 1.34-1.44(m, 2H), 1.2-1.3(m, 8H), 1.20(s, 6H), 1.19(s, 6H), 0.86(t, $J=7\text{Hz}$, 3H)

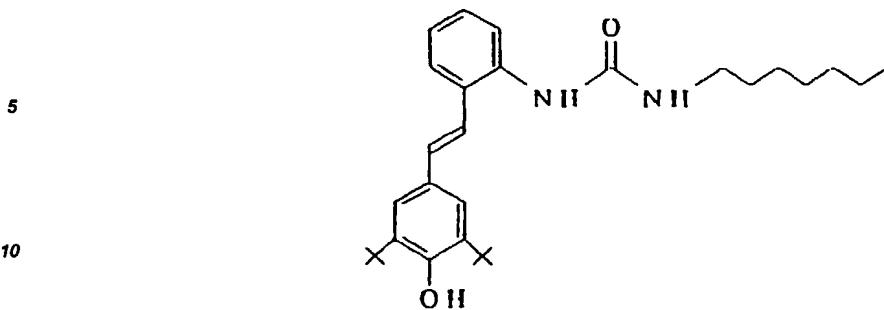
IR (cm^{-1}) 3330, 2960, 2930, 1640, 1580, 1470, 1450, 1260, 750

Example 48

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N-[2-(3,5-di-tert-butyl-4-hydroxystyryl)phenyl]-N'-heptylurea

55



A solution of diphenylphosphoryl azide (0.36 g, 1.3 mmol), octanoic acid (0.17 g, 1.2 mmol) and triethylamine (0.13 g, 1.3 mmol) in toluene (5 ml) was stirred at room temperature for 1.5 hrs and further stirred at about 90°C for 2 hrs. After allowing the mixture to cool, a solution of 4-(2-aminostyryl)-2,6-di-tert-butylphenol (0.89 g, 1.2 mmol) in toluene (2 ml) was added dropwise under ice-cooling while stirring. The reaction solution was returned slowly to room temperature and stirred overnight. The solvent was distilled off, the residue was purified by a silica gel column chromatography and recrystallized from ethyl acetate/hexane to give crystals of the title compound (0.39 g, 70%). m.p. 162-164°C

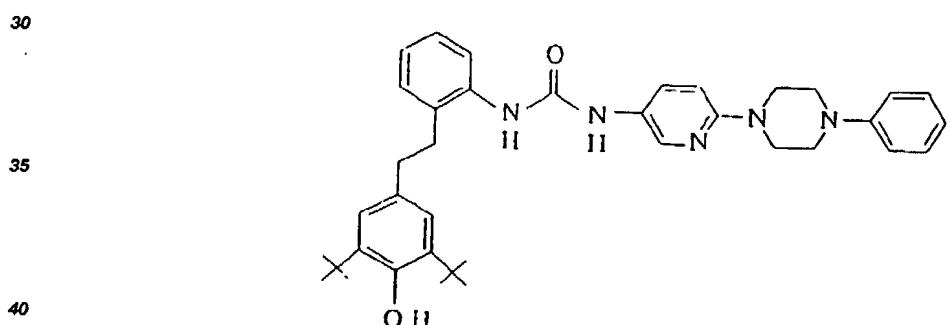
¹H-NMR(δ ppm, CDCl₃) 7.63(dd, J=7, 2Hz, 1H), 7.33-7.37(m, 3H), 7.21-7.28(m, 2H), 7.08(d, J=16Hz, 1H), 7.01(d, J=16Hz, 1H), 6.01(bs, 1H), 5.33(s, 1H), 4.54(t, J=6Hz, 1H), 3.20(dt, J=6, 7Hz, 2H), 1.42-1.47(m, 20H), 1.20-1.36(m, 8H), 0.83(t, J=7Hz, 3H)

IR (cm⁻¹) 3626, 3334, 2954, 2926, 1642, 1568, 1454, 1439, 1235, 1152, 960, 751

25

Example 49

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(2-(4-phenyl-1-piperadiny)-5-pyridyl)urea



The title compound was prepared in a similar manner to that mentioned in Example 1, using 6-(4-phenyl-1-piperadiny)nicotinic acid instead of 4-hexyloxybenzoic acid. m.p. 197-199°C

45

1H-NMR(δ ppm, CDCl₃) 7.95(d, J=2Hz, 1H), 7.67(dd, J=9, 2Hz, 1H), 7.39(d, J=9Hz, 1H), 7.17-7.33(m, 5H), 6.94-7.00(m, 2H), 6.89(dd, J=7, 7Hz, 1H), 6.81(s, 2H), 6.65(d, J=9Hz, 1H), 5.85(bs, 1H), 5.22(bs, 1H), 5.16(s, 1H), 3.62(t, J=5Hz, 4H), 3.28(t, J=5Hz, 4H), 2.76-2.92(m, 4H), 1.38(s, 18H)

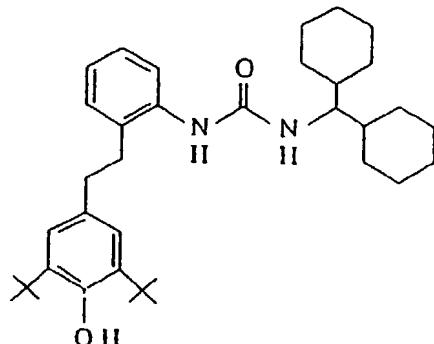
IR(cm⁻¹) 3620, 3330, 3290, 2954, 1646, 1600, 1547, 1492, 1233, 951, 760

50 Example 50

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(dicyclohexylmethyl)urea

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5



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The title compound was prepared in a similar manner to that mentioned in Example 1, using dicyclohexylacetic acid instead of 4-hydroxybenzoic acid. m.p. 94-195°C

¹H-NMR(δ ppm, CDCl₃) 7.29-7.18(m, 4H), 6.81(s, 2H), 5.19(bs, 1H), 5.09(s, 1H), 4.00(d, J=10Hz, 1H), 3.47(bs, 1H), 2.88(t, J=7Hz, 2H), 2.80(t, J=7Hz, 2H), 1.54-1.70(m, 10H), 1.38(s, 18H), 1.38-1.42(m, 2H), 1.01-1.19(m, 8H), 0.73-0.80(m, 2H)

IR(cm⁻¹) 3642, 3362, 2924, 2852, 1641, 1553, 1436, 1235, 744

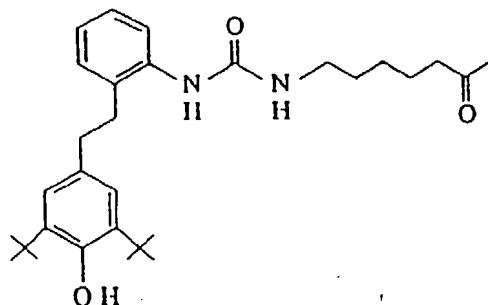
20

Example 51

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(6-oxooctanoic acid)urea

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The title compound was prepared in a similar manner to that mentioned in Example 1, using 7-oxooctanoic acid instead of 4-hydroxybenzoic acid. m.p. 73-76°C

¹H-NMR(δ ppm, CDCl₃) 7.16-7.25(m, 4H), 6.77(s, 2H), 5.12(s, 1H), 4.97(s, 1H), 4.17-4.24(m, 1H), 3.12(td, J=7, 6Hz, 2H), 2.76-2.86(m, 4H), 2.38(t, J=7Hz, 2H), 2.10(s, 3H), 1.49-1.57(m, 2H), 1.33-1.45(m, 4H), 1.37(s, 18H)

IR(cm⁻¹) 3368, 2950, 1712, 1632, 1574

45

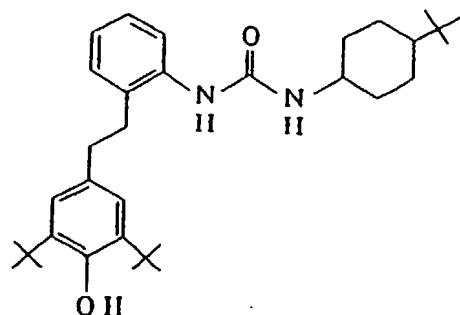
Example 52

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(4-tert-butylcyclohexyl)urea

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15 The title compound was prepared in a similar manner to that mentioned in Example 1, using 4-tert-butylcyclohexanecarboxylic acid instead of 4-hexyloxybenzoic acid. m.p. 206-208°C

1H-NMR(δ ppm, CDCl_3) 7.15-7.25(m, 4H), 6.78(s, 2H), 5.10(s, 1H), 5.00(s, 1H), 4.02(d, $J=8\text{Hz}$, 1H), 3.47-3.57(m, 1H), 2.76-2.86(m, 4H), 1.96-1.98(m, 2H), 1.70-1.73(m, 2H), 1.38(s, 18H), 0.84-1.13(m, 5H), 0.81(s, 9H)

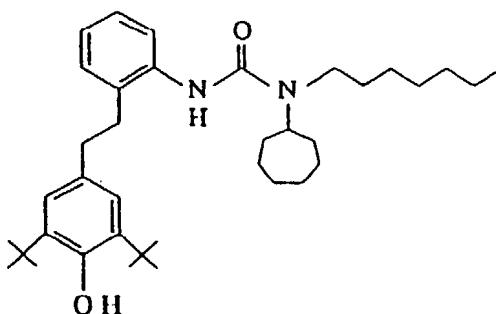
20 IR(cm^{-1}) 3642, 3356, 2948, 1640, 1585, 1436, 1234

Example 53

25 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-cycloheptyl-N'-heptylurea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using N-heptylcycloheptylamine instead of decylamine. m.p. 70-72°C

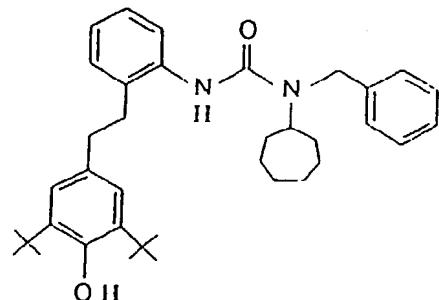
1H-NMR(δ ppm, CDCl_3) 7.77(dd, $J=8, 1\text{Hz}$, 1H), 7.20(ddd, $J=8, 8, 2\text{Hz}$, 1H), 7.13(dd, $J=8, 1\text{Hz}$, 1H), 7.02(ddd, $J=8, 8, 1\text{Hz}$, 1H), 6.89(s, 2H), 6.04(s, 1H), 5.06(s, 1H), 4.02(bs, 1H), 3.07-3.11(m, 2H), 2.82(s, 4H), 1.82-1.87(m, 2H), 1.58-1.70(m, 8H), 1.40-1.56(m, 4H), 1.40(s, 18H), 1.25(bs, 8H), 0.84-0.90(m, 3H)

IR(cm^{-1}) 3642, 3296, 2910, 1631, 1588, 1435, 1235, 751

Example 54

55 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-benzyl-N'-cycloheptylurea

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20

The title compound was prepared in a similar manner to that mentioned in Example 11, using benzylcycloheptylamine instead of decylamine. m.p. 183-184°C

¹H-NMR(δ ppm, CDCl₃) 7.74(d, J=8Hz, 1H), 7.25-7.30(m, 2H), 7.07-7.21(m, 4H), 6.90-6.93(m, 2H), 6.76(s, 2H), 5.95(s, 1H), 5.06(s, 1H), 4.42-4.50(m, 1H), 4.43(s, 2H), 2.52(t, J=8Hz, 2H), 2.23(t, J=8Hz, 2H), 1.92-1.99(m, 2H), 1.43-1.72(s, 10H), 1.42(s, 18H)

IR(cm⁻¹) 3638, 3402, 2926, 1671, 1589, 1527, 1455, 1232, 1213, 752

25

Example 55

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-(4-dimethylaminophenyl)cyclopentyl)methyl]urea

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35

The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-[1-(aminomethyl)cyclopentyl]-N,N-dimethylaniline instead of decylamine. m.p. 174-175°C

¹H-NMR(δ ppm, CDCl₃) 7.08-7.21(m, 3H), 7.03(d, J=7Hz, 1H), 6.92(d, J=9Hz, 2H), 6.77(s, 2H), 6.54(d, J=8Hz, 2H), 5.07(s, 2H), 4.07-4.15(m, 1H), 3.22(d, J=5Hz, 2H), 2.88(s, 6H), 2.69-2.79(m, 4H), 1.63-1.83(m, 8H), 1.36(s, 18H)

IR(cm⁻¹) 3640, 3360, 1644, 1525, 1435, 1233, 814, 749

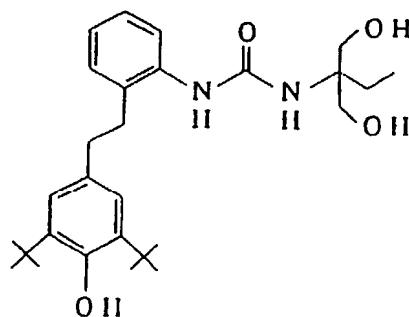
45

Example 56

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(2-ethyl-1,3-dihydroxy-2-propyl)urea

50

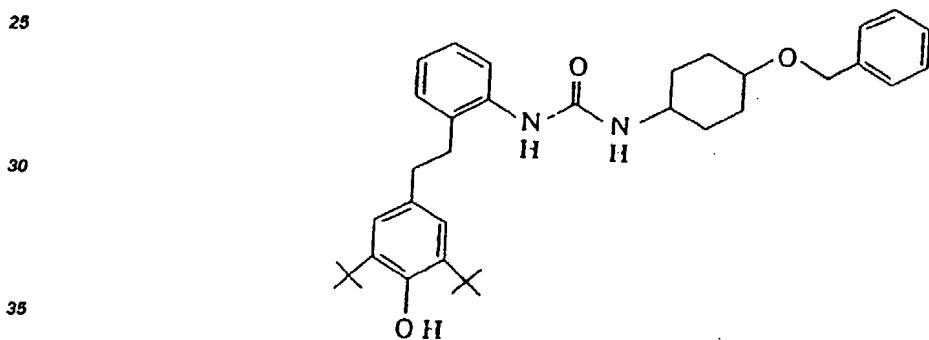
55



The title compound was prepared in a similar manner to that mentioned in Example 11, using 2-amino-2-ethyl-1,3-propanediol instead of decylamine. m.p. 145-146°C
¹H-NMR(δ ppm, CDCl₃) 7.16-7.31(m, 4H), 6.78(s, 2H), 5.12(s, 1H), 5.11(s, 1H), 4.61(s, 1H), 3.75-3.89(m, 4H), 3.46-3.55(m, 2H), 2.75-2.88(m, 4H), 1.51(q, J=8Hz, 2H), 1.38(s, 18H), 0.75(t, J=8Hz, 3H)
IR(cm⁻¹) 3640, 3570, 3400, 3340, 2970, 1660, 1610, 1560, 1440, 1250, 750, 650

25 Example 57

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(4-benzyloxycyclopropyl)urea



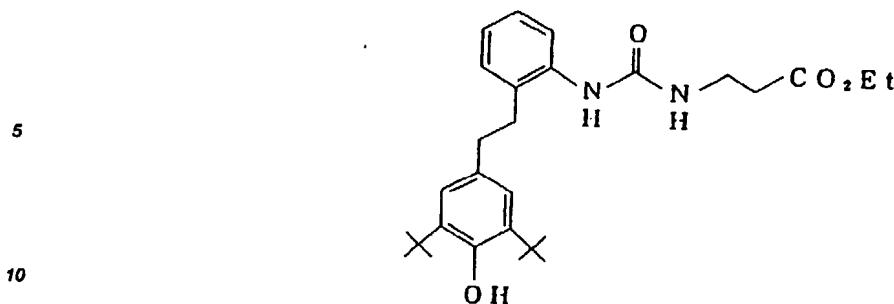
The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-benzyloxycyclohexylamine instead of decylamine.
40 m.p. 152-153°C
¹H-NMR(δ ppm, CDCl₃) 7.16-7.36(m, 9H), 6.77(s, 2H), 5.11(s, 1H), 4.94(s, 1H), 4.51(s, 2H), 4.00(d, J=8Hz, 1H), 3.56-3.68(m, 1H), 3.18-3.28(m, 1H), 2.74-2.86(m, 4H), 1.93-2.15(m, 4H), 1.31-1.47(m, 2H), 1.38(s, 18H), 0.94-1.08(m, 2H)
IR(cm⁻¹) 3630, 3370, 3330, 2950, 1645, 1565, 1235, 1090, 750

45 Example 58

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(2-ethoxycarbonylethyl)urea

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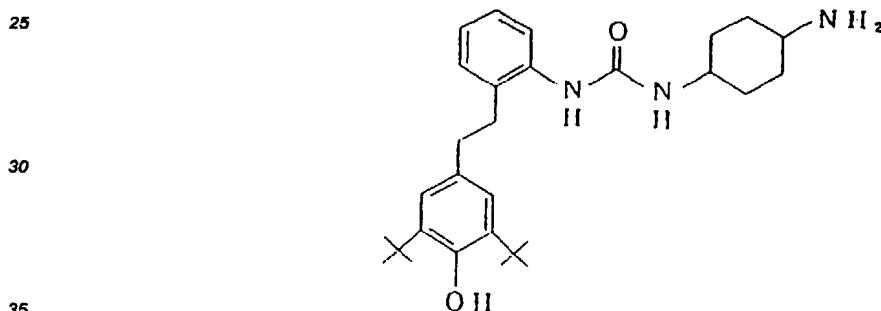


The title compound was prepared in a similar manner to that mentioned in Example 11, using ethyl 3-aminopropionate instead of decylamine. m.p. 158-159°C

15 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.14-7.28(m, 4H), 6.78(s, 2H), 5.12(s, 1H), 5.08(s, 1H), 4.75(t, $J=6\text{Hz}$, 1H), 4.07(q, $J=7\text{Hz}$, 2H), 3.41(dt, $J=6, 6\text{Hz}$, 1H), 2.74-2.86(m, 4H), 2.49(t, $J=6\text{Hz}$, 2H), 1.38(18H.s, 18H), 1.18(t, $J=7\text{Hz}$, 3H)
 IR(cm^{-1}) 3630, 3320, 3270, 2960, 1730, 1630, 1570, 1440, 1235, 1190, 745

20 Example 59

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(4-aminocyclohexyl)urea



The title compound was prepared in a similar manner to that mentioned in Example 11, using 1,4-diaminocyclohexane instead of decylamine.

m.p. >280°C (dec.)

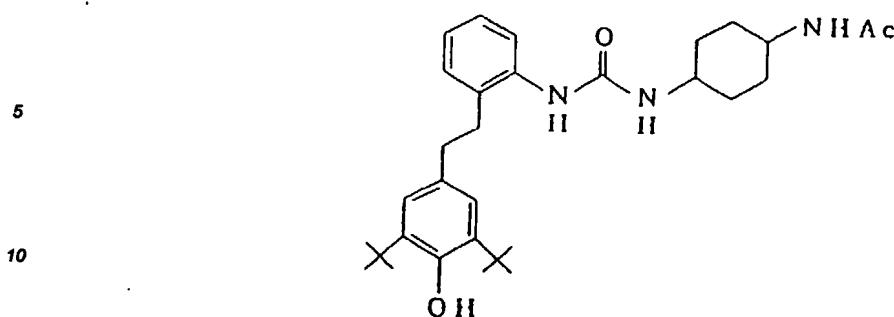
40 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.14-7.28(m, 4H), 6.77(s, 2H), 5.12(bs, 1H), 4.97(bs, 1H), 3.98-4.05(m, 1H), 3.53-3.64(m, 1H), 2.74-2.87(m, 4H), 2.52-2.62(m, 1H), 1.89-1.97(m, 2H), 1.77-1.86(m, 2H), 1.38(s, 18H), 0.97-1.24(m, 4H)
 IR(cm^{-1}) 3630, 3420, 3340, 2940, 1635, 1590, 1570, 1240, 935

45 Example 60

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(4-acetamidocyclohexyl)urea

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55



15 The title compound was prepared in a similar manner to that mentioned in Example 11, using N-(4-aminocyclohexyl)acetamide instead of decylamine.

m.p. 250°C (dec.)

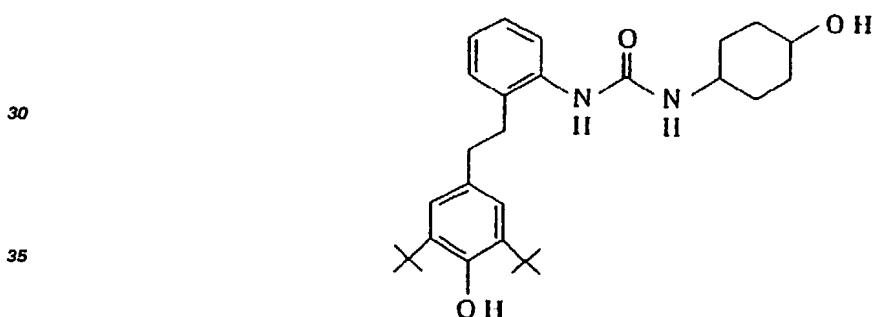
1H-NMR(δ ppm, CDCl₃) 7.16-7.30(m, 4H), 6.77(s, 2H), 5.26(bd, J=8Hz, 1H), 5.11(s, 1H), 4.93(s, 1H), 4.05(d, J=8Hz, 1H), 3.54-3.73(m, 2H), 2.74-2.87(m, 4H), 1.92-2.00(m, 4H), 1.93(s, 3H), 1.37(s, 18H), 1.03-1.27(m, 4H)

20 IR(cm⁻¹) 3640, 3290, 2950, 1635, 1550, 1440, 1235, 760

Example 61

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(4-hydroxycyclohexyl)urea

25



40 The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-aminocyclohexanol instead of decylamine. m.p. 202-203°C

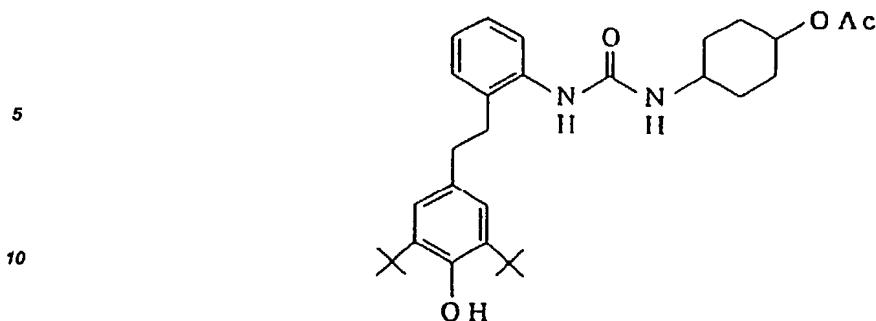
1H-NMR(δ ppm, CDCl₃) 7.17-7.29(m, 4H), 6.77(s, 2H), 5.12(s, 1H), 4.94(s, 1H), 3.99(d, J=8Hz, 1H), 3.43-3.69(m, 2H), 2.75-2.87(m, 4H), 1.87-2.01(m, 4H), 1.28-1.43(m, 2H), 1.38(s, 18H), 0.97-1.12(m, 2H)
IR(cm⁻¹) 3645, 3320, 2950, 1640, 1570, 1440, 1235, 1070, 880, 745

45 Example 62

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(4-acetoxy cyclohexyl)urea

50

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15 The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-aminocyclohexyl acetate instead of decylamine. m.p. 92-94°C

¹H-NMR(δ ppm, CDCl₃) 7.17-7.28(m, 4H), 6.77(s, 2H), 5.12(s, 1H), 4.93(s, 1H), 4.53-4.64(m, 1H), 4.02(d, J =8Hz, 1H), 3.57-3.71(m, 1H), 2.78-2.87(m, 4H), 2.01(s, 3H), 1.87-2.02(m, 4H), 1.32-1.52(m, 2H), 1.38(s, 18H), 1.02-1.16(m, 2H)

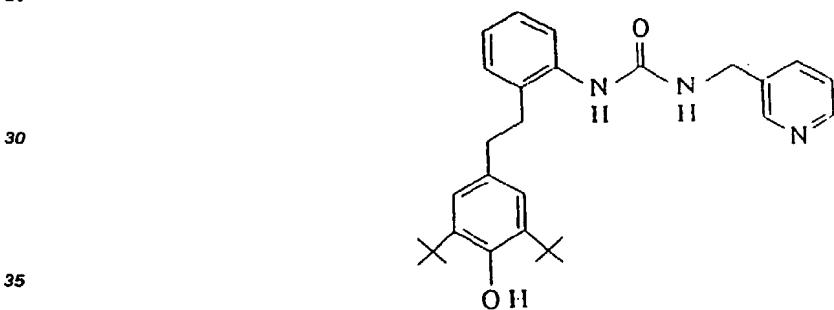
IR(cm^{-1}) 3640, 3380, 2960, 1740, 1645, 1560, 1440, 1245, 1050, 765

20

Example 63

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(3-pyridylmethyl)urea

28



The title compound was prepared in a similar manner to that mentioned in Example 11, using 3-(amino-methyl)pyridine instead of decylamine. m.p. 163-164°C

⁴⁰ ¹H-NMR(δ ppm, CDCl₃) 8.48(dd, J=5, 1Hz, 1H), 8.45(d, J=2Hz, 1H), 7.58(d, J=8Hz, 1H), 7.18-7.27(m, 5H), 6.75(s, 2H), 5.12(s, 1H), 4.95(s, 1H), 4.45-4.50(m, 1H), 4.34(d, J=6Hz, 2H), 2.75-2.86(m, 4H), 1.35(s, 18H)
IR(cm⁻¹) 3294, 1634, 1574, 1430, 1239, 1119, 760, 712

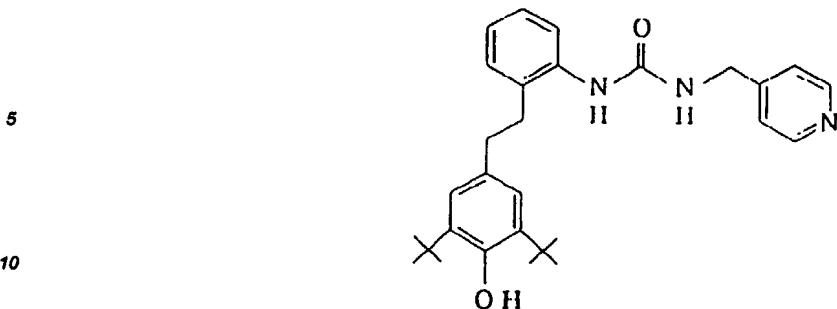
Example 64

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N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(4-pyridylmethyl)urea

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55

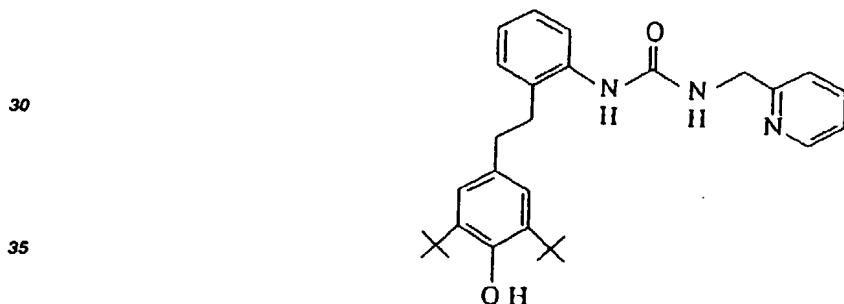


15 The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-(amino-methyl)pyridine instead of decylamine. m.p. 214-215°C
¹H-NMR(δ ppm, CDCl₃) 8.50(dd, J=4, 1Hz, 2H), 7.30-7.25(m, 2H), 7.20-7.24(m, 2H), 7.12(d, J=6Hz, 2H),
6.77(s, 2H), 5.13(s, 1H), 5.00(s, 1H), 4.54(t, J=6Hz, 1H), 4.34(d, J=6Hz, 2H), 2.86-2.90(m, 2H), 2.79-2.82(m, 2H), 1.35(s, 18H)
20 IR(cm⁻¹) 3292, 1632, 1573, 1436, 1237, 761

Example 65

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(2-pyridylmethyl)urea

25



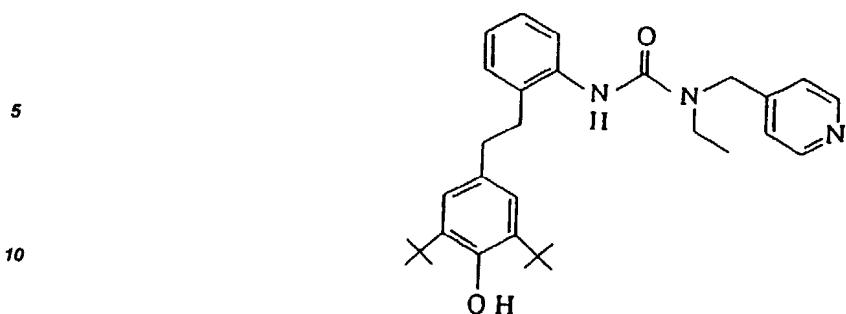
40 The title compound was prepared in a similar manner to that mentioned in Example 11, using 2-(amino-methyl)pyridine instead of decylamine. m.p. 189-190°C
¹H-NMR(δ ppm, CDCl₃) 8.42(dd, J=4, 1Hz, 1H), 7.61(ddd, J=8, 8, 2Hz, 1H), 7.38(dd, J=8, 1Hz, 1H), 7.12-
7.24(m, 5H), 6.80(s, 2H), 5.48(bs, 1H), 5.36(t, J=5Hz, 1H), 5.29(s, 1H), 4.47(d, J=6Hz, 2H), 2.78-2.89(m, 4H),
1.36(s, 18H)
45 IR(cm⁻¹) 3632, 3612, 3296, 1627, 1576, 1437, 1234, 755

Example 66

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-ethyl-N'-(4-pyridylmethyl)urea

50

55

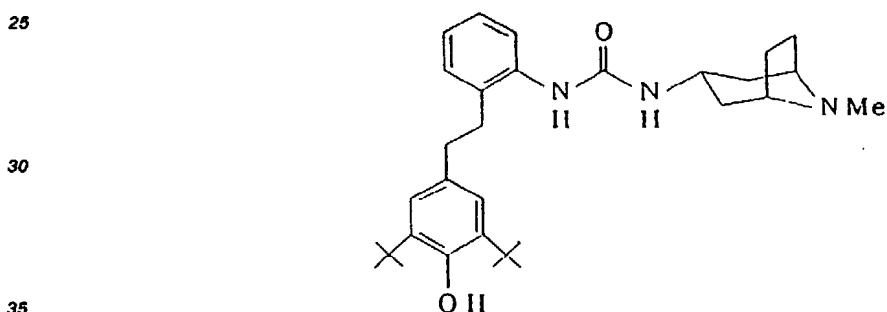


15 The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-(ethylaminomethyl)pyridine instead of decylamine.

1H-NMR(δ ppm, CDCl₃) 8.51(dd, J=4, 1Hz, 2H), 7.66(dd, J=8, 1Hz, 1H), 7.09-7.25(m, 5H), 6.79(s, 2H), 5.85(s, 1H), 5.09(s, 1H), 4.50(s, 2H), 3.09(q, J=7Hz, 2H), 2.74-2.82(m, 4H), 1.36(s, 18H), 1.14(t, J=7Hz, 3H)
IR(cm⁻¹) 3266, 3080, 1630, 1606, 1516, 1492, 1451, 1431, 1269, 755, 746

20 Example 67

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(8-methyl-8-azabicyclo[3.2.1]-3-octyl)urea



35 The title compound was prepared in a similar manner to that mentioned in Example 11, using 3-amino-8-methyl-8-azabicyclo[3.2.1]octane instead of decylamine.

m.p. 229-230°C

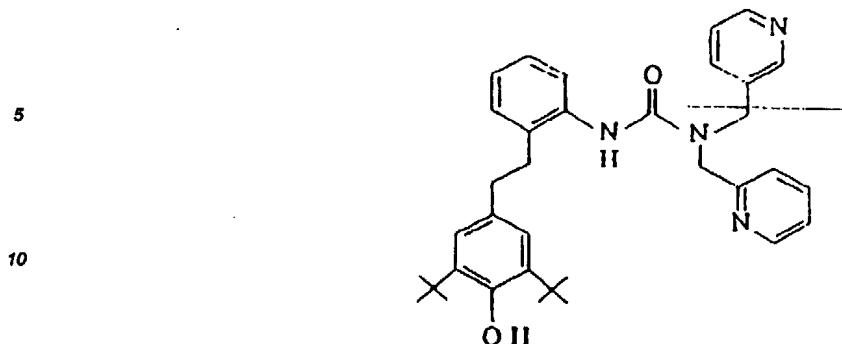
40 1H-NMR(δ ppm, CDCl₃) 7.27(d, J=4Hz, 1H), 7.13-7.21(m, 3H), 6.79(s, 2H), 5.51(bs, 1H), 5.14(s, 1H), 4.77(bs, 1H), 4.07-4.13(m, 1H), 3.51(bs, 2H), 2.76-2.87(m, 4H), 2.51(s, 3H), 2.13-2.15(m, 2H), 1.89-1.96(m, 6H), 1.38(m, 18H)
IR(cm⁻¹) 3360, 1645, 1565, 1435, 1240, 745

45 Example 68

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(2-pyridylmethyl)-N'-(3-pyridylmethyl)urea

50

55

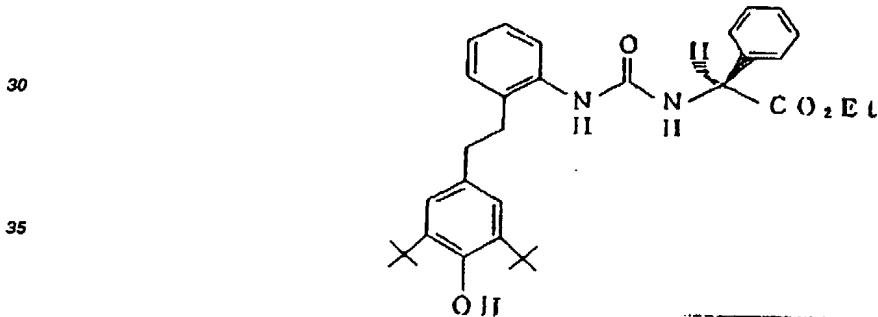


1H-NMR(δ ppm, CDCl_3) 9.47(s, 2H), 8.52(d, $J=4\text{Hz}$, 1H), 8.48(dd, $J=5, 1\text{Hz}$, 1H), 7.89(d, $J=6\text{Hz}$, 1H), 7.76(dd, $J=8, 1\text{Hz}$, 1H), 7.67(dd, $J=8, 2\text{Hz}$, 1H), 7.54(dd, $J=8, 2\text{Hz}$, 1H), 7.23(t, $J=7\text{Hz}$, 2H), 7.14-7.18(m, 1H), 7.02-7.06(m, 2H), 6.97(d, $J=8\text{Hz}$, 1H), 6.93(s, 2H), 5.19(s, 1H), 4.60(s, 2H), 4.37(s, 2H), 2.96-3.05(m, 2H), 2.90-2.94(m, 2H), 1.35(s, 18H)

IR(cm^{-1}) 3632, 3250, 1661, 1591, 1533, 1480, 1436, 1393, 1362, 1295, 1214, 755

Example 69

25 (S)-N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(α -ethoxycarbonyl)benzylurea

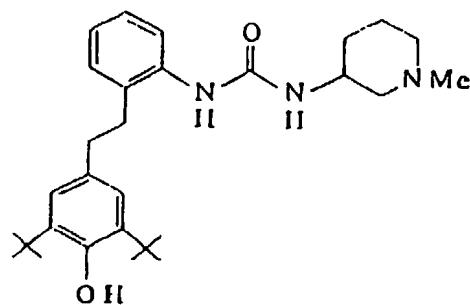


1H-NMR(δ ppm, CDCl_3) 7.44(d, $J=8\text{Hz}$, 1H), 7.19-7.33(m, 8H), 6.78(s, 2H), 5.90(s, 1H), 5.74(d, $J=7\text{Hz}$, 1H), 5.59(d, $J=8\text{Hz}$, 1H), 5.16(s, 1H), 4.10-4.24(m, 2H), 2.89-2.92(m, 2H), 2.82-2.85(m, 2H), 1.43(s, 18H), 1.21(t, $J=7\text{Hz}$, 3H)

45 IR(cm^{-1}) 3636, 3294, 1737, 1643, 1542, 1435, 1233, 1181, 754

Example 70

50 N-[2(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-methyl-3-piperidyl)urea

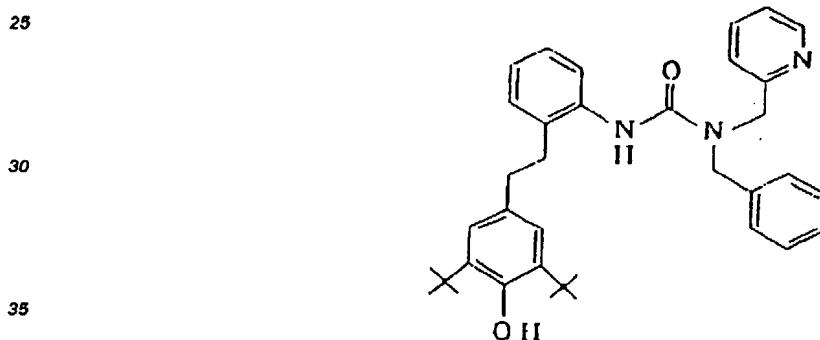


The title compound was prepared in a similar manner to that mentioned in Example 11, using 3-amino-1-methylpiperidine instead of decylamine.

15 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.45(d, $J=8\text{Hz}$, 1H), 7.16-7.26(m, 3H), 6.92(s, 2H), 6.35(bs, 1H), 5.40(bs, 1H), 5.17(s, 1H), 3.45(bs, 1H), 3.18-3.23(m, 1H), 2.93-3.01(m, 1H), 2.83-2.92(m, 4H), 2.45-2.51(m, 1H), 2.34(s, 3H), 2.18-2.27(m, 1H), 1.82-1.95(m, 1H), 1.60-1.73(m, 3H), 1.46(s, 18H)
 IR(cm^{-1}) 3638, 3250, 1643, 1548, 1436, 1235, 910, 733

20 Example 71

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-benzyl-N-(2-pyridylmethyl)urea



The title compound was prepared in a similar manner to that mentioned in Example 11, using N-benzyl-2-pyridylmethylamine instead of decylamine.

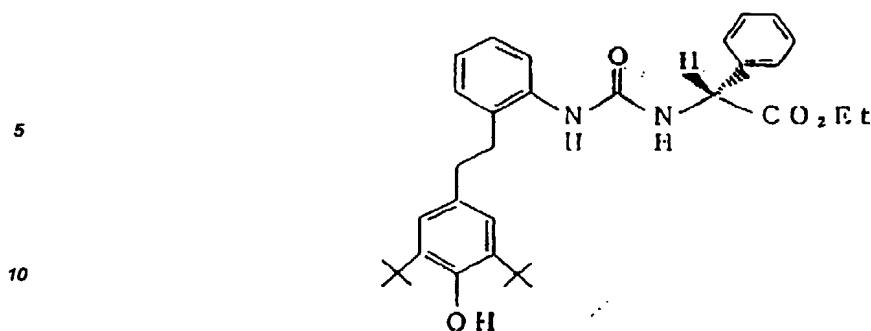
40 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 9.20(bs, 1H), 7.92(d, $J=4\text{Hz}$, 1H), 7.78(d, $J=7\text{Hz}$, 1H), 7.52(ddd, $J=8, 8, 2\text{Hz}$, 1H), 7.19-7.30(m, 7H), 7.01-7.05(m, 2H), 6.93(s, 2H), 6.92-6.94(m, 1H), 5.06(s, 1H), 4.60(s, 2H), 4.41(s, 2H), 2.88-3.00(m, 4H), 1.36(s, 18H)
 IR(cm^{-1}) 3620, 3250, 2244, 1657, 1590, 1532, 1453, 1436, 1213, 752, 732

45 Example 72

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(α -ethoxycarbonyl)benzylurea

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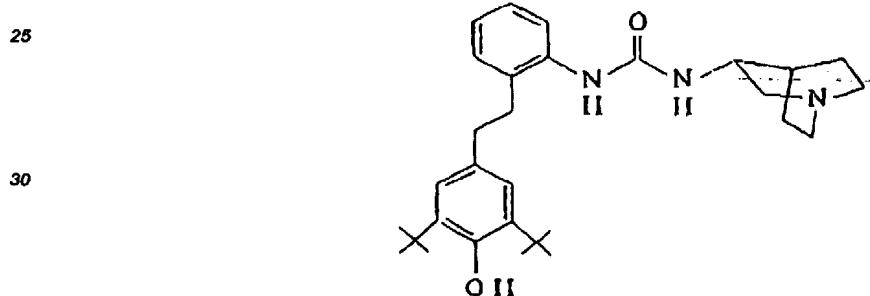


15 The title compound was prepared in a similar manner to that mentioned in Example 11, using (R)- α -phenylglycine ethyl ester instead of decylamine.

1H-NMR(δ ppm, CDCl₃) 7.18-7.35(m, 9H), 6.77(s, 2H), 5.50(d, J=8Hz, 1H), 5.37(d, J=8Hz, 1H), 5.33(s, 1H), 5.09(s, 1H), 4.07-4.18(m, 2H), 2.78-2.84(m, 4H), 1.35(s, 18H), 1.17(t, J=7Hz, 3H)
IR(cm⁻¹) 3636, 3330, 1739, 1640, 1542, 1436, 1234, 1180, 935, 751, 698

20 Example 73

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-azabicyclo[2.2.2]-3-octyl)urea



35 The title compound was prepared in a similar manner to that mentioned in Example 11, using 3-amino-1-azabicyclo[2.2.2]octane instead of decylamine.

m.p. 227-229°C

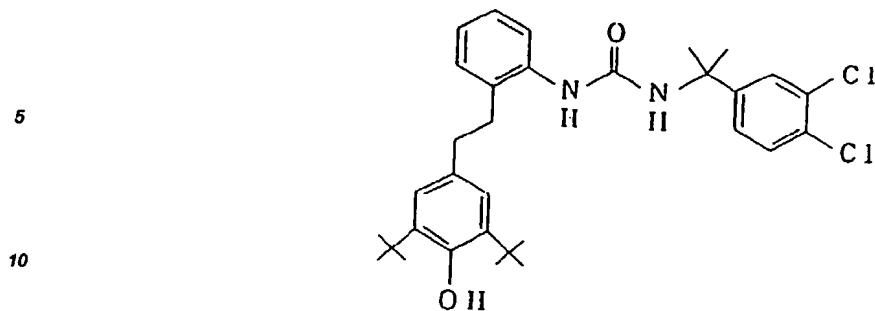
40 1H-NMR(δ ppm, CDCl₃) 7.21-7.27(m, 4H), 6.77(s, 2H), 5.11(s, 1H), 5.07(s, 1H), 4.43(d, J=7Hz, 1H), 3.78-3.85(m, 1H), 3.28(dd, J=14, 10, 2Hz, 1H), 2.65-2.89(m, 8H), 2.29-2.33(m, 1H), 1.85-1.87(m, 1H), 1.55-1.70(m, 4H), 1.38(s, 18H)
IR(cm⁻¹) 3636, 3368, 3260, 1640, 1587, 1564, 1434, 1237, 1122, 765, 753

45 Example 74

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[2-(3,4-dichlorophenyl)-2-propyl]urea

50

55



15 The title compound was prepared in a similar manner to that mentioned in Example 11, using 3,4-dichloro-
 α,α -dimethylbenzylamine instead of decylamine.
m.p. 203-205°C.

1H-NMR/

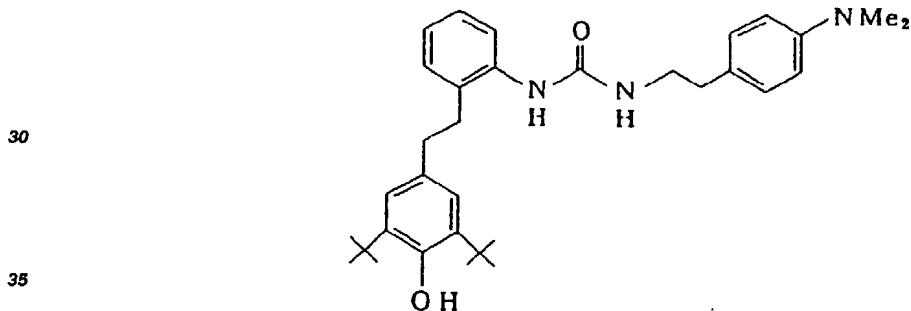
¹H-NMR (δ, ppm, CDCl₃) 7.41(d, J=2Hz, 1H), 7.16-7.32(m, 6H), 6.81(s, 2H), 5.17(s, 1H), 5.11(s, 1H), 4.60(s, 1H), 2.79-2.83(m, 4H), 1.56(s, 6H), 1.39(s, 18H)

20

Example 75

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(4-dimethylaminophenethyl)urea

23



The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-dimethylaminophenethylamine instead of decylamine.

40

¹H-NMR(δ ppm, CDCl₃) 7.11-7.24(m, 4H), 6.96(d, J =9Hz, 2H), 6.77(s, 2H), 6.62(s, 2H), 5.09(s, 1H), 5.08(s, 1H), 4.03(t, J =6Hz, 1H), 3.33(td, J =7, 6Hz, 2H), 2.89(s, 6H), 2.72-2.86(m, 4H), 2.64(t, J =7Hz, 2H), 1.37(s, 18H)

IR(cm⁻¹) 3640, 3342, 2940, 1640, 1562, 1521, 1439, 1232, 660, 643

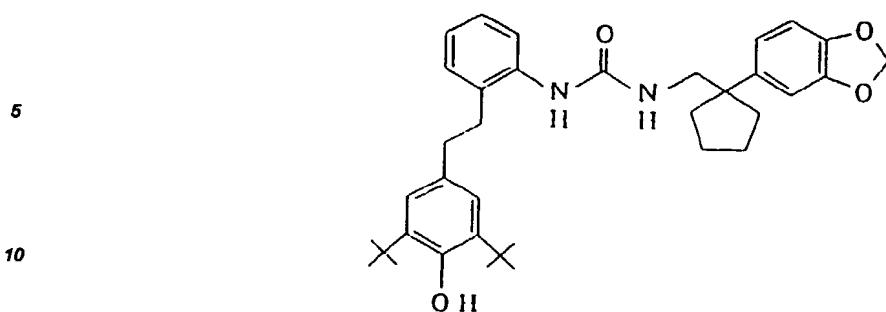
45

Example 76

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[1-(3,4-methylenedioxyphenyl)cyclopentyl]methyl]urea

50

55

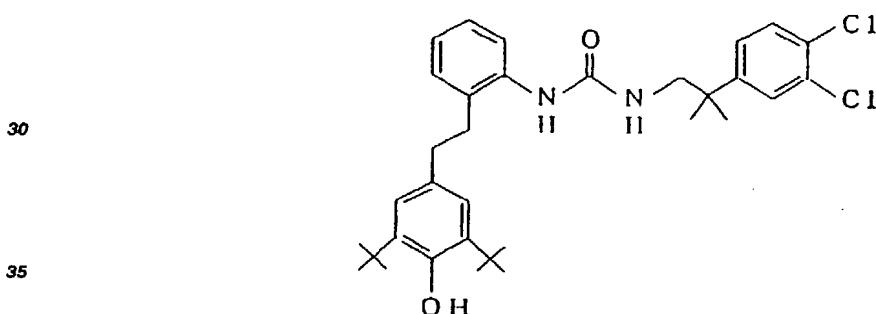


15 The title compound was prepared in a similar manner to that mentioned in Example 11, using 5-[1-(aminomethyl)cyclopentyl]-1,3-dioxaindane instead of decylamine. m.p. 188-189°C
 1H-NMR(δ ppm, CDCl₃) 7.12-7.22(m, 3H), 7.03(d, J=7Hz, 1H), 6.75(s, 2H), 6.59(d, J=2Hz, 1H), 6.57(d, J=8Hz, 1H), 6.47(dd, J=8, 2Hz, 1H), 5.88(s, 2H), 5.08(s, 1H), 5.00(s, 1H), 3.95-4.00(m, 1H), 3.21(d, J=5Hz, 2H), 2.70-2.80(m, 4H), 1.55-1.85(m, 8H), 1.36(s, 18H)
 IR(cm⁻¹) 3640, 3388, 3328, 1645, 1561, 1488, 1435, 1363, 1234, 1042, 940, 760

20 Example 77

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(2-(3,4-dichlorophenyl)-2-methylpropyl)urea

25



40 The title compound was prepared in a similar manner to that mentioned in Example 11, using 3,4-dichloro- β,β -dimethylphenethylamine instead of decylamine.

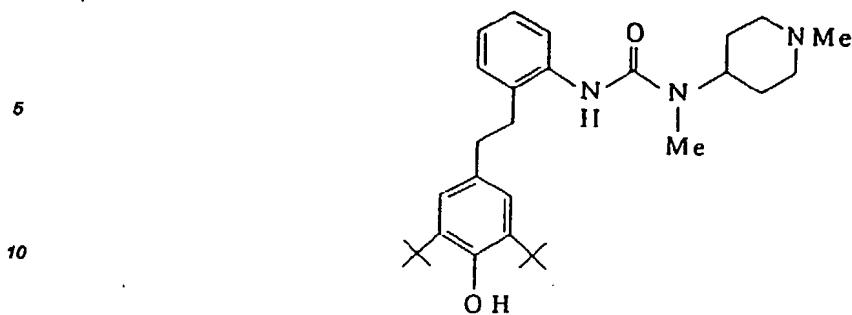
m.p. 165-167°C
 1H-NMR(δ ppm, CDCl₃) 6.95-7.29(m, 7H), 6.73(s, 2H), 5.09(s, 1H), 4.90-5.00(m, 1H), 3.96(bs, 1H), 3.29(d, J=6Hz, 2H), 2.65-2.75(m, 4H), 1.35(s, 18H), 1.23(s, 6H)
 IR(cm⁻¹) 3638, 3364, 1646, 1587, 1563, 1475, 1437, 1235, 762

45 Example 78

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-methyl-N'-(1-methyl-4-piperidyl)urea

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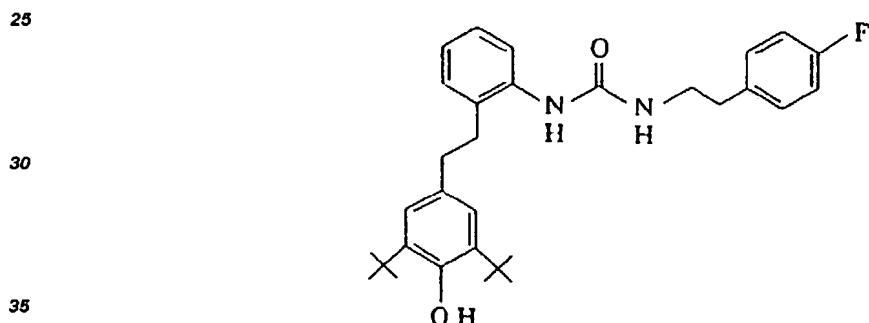
The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-methyl-4-(methylamino)piperidine instead of decylamine.

15 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.63(d, $J=7\text{Hz}$, 1H), 7.19-7.26(m, 2H), 7.10(dd, $J=7, 7, 1\text{Hz}$, 1H), 6.79(s, 2H), 5.63(s, 1H), 5.08(s, 1H), 4.20-4.27(m, 1H), 2.85-2.90(m, 2H), 2.82(s, 4H), 2.48(s, 3H), 2.28(s, 3H), 1.98-2.07(m, 2H), 1.55-1.90(m, 4H), 1.35(s, 18H)

20 IR(cm^{-1}) 3424, 1638, 1511, 1484, 1450, 1436, 1287, 1042, 754

25 Example 79

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(4-fluorophenethyl)urea



The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-fluorophenethylamine instead of decylamine. m.p. 177-179°C

40 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.03-7.26(m, 6H), 6.89-6.93(m, 2H), 6.76(m, 2H), 5.10(s, 1H), 4.94(s, 1H), 4.15-4.20(m, 1H), 3.35(q, $J=7\text{Hz}$, 2H), 2.76-2.82(m, 4H), 2.71(t, $J=7\text{Hz}$, 2H), 1.36(s, 18H)

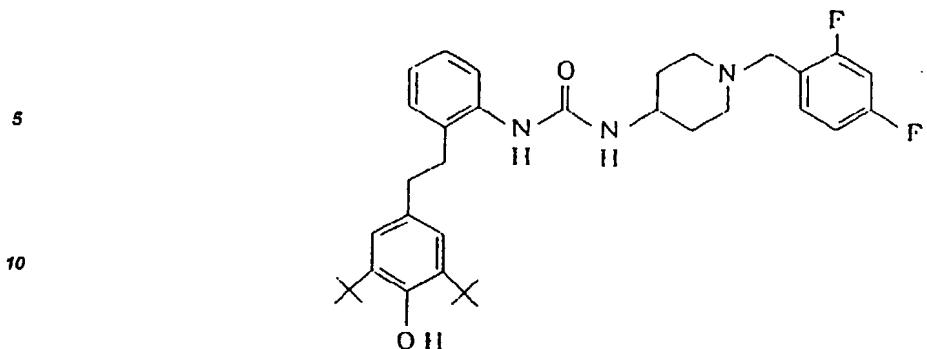
IR(cm^{-1}) 3636, 3348, 1643, 1563, 1511, 1438, 1234, 831, 747

45 Example 80

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-(2,4-difluorobenzyl)-4-piperidyl)urea

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15 The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-amino-1-(2,4-difluorobenzyl)pyperidine instead of decylamine.

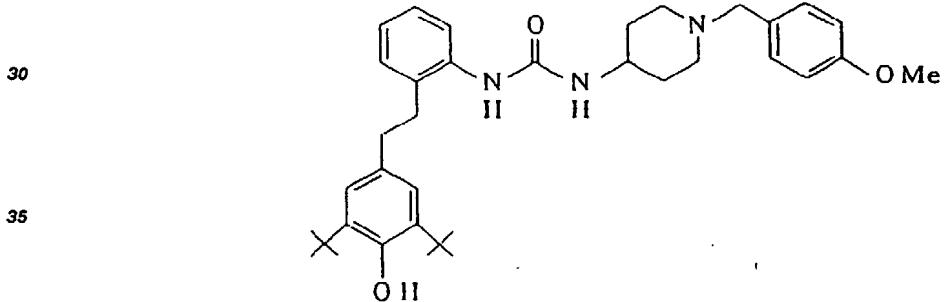
m.p. 157-158°C

1H-NMR(δ ppm, CDCl₃) 7.15-7.36(m, 5H), 6.89-6.72(m, 4H), 5.11(s, 1H), 4.97(s, 1H), 4.09(d, J=8Hz, 1H), 3.57-3.72(m, 1H), 3.47(s, 2H), 2.68-2.88(m, 6H), 2.14-2.20(m, 2H), 1.82-1.95(m, 2H), 1.58-1.74(m, 2H), 1.20-1.40(m, 2H), 1.37(s, 18H)

20 IR(cm⁻¹) 3640, 3370, 3250, 2960, 1690, 1650, 1590, 1565, 1505, 1235, 850, 760

Example 81

25 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-(4-methoxybenzyl)-4-piperidyl)urea



40 The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-amino-1-(4-methoxybenzyl)piperidine instead of decylamine.

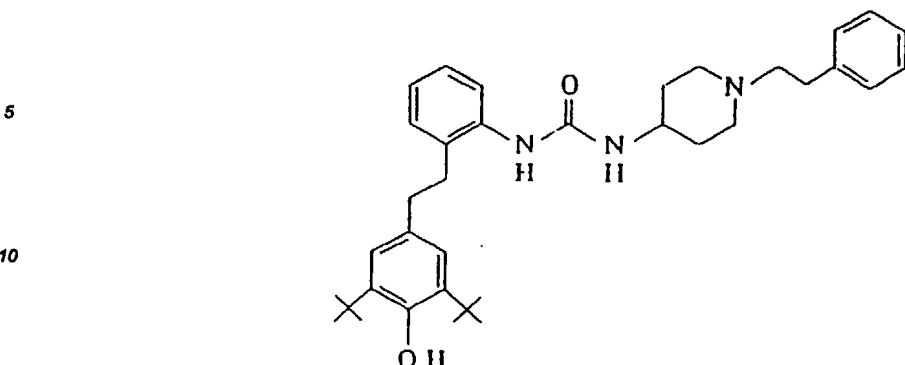
m.p. 152-153°C

1H-NMR(δ ppm, CDCl₃) 7.14-7.30(m, 6H), 6.74-6.88(m, 4H), 5.11(s, 1H), 4.97(s, 1H), 4.09(d, J=8Hz, 1H), 3.79(s, 3H), 3.56-3.72(m, 1H), 3.38(s, 2H), 2.67-2.88(m, 6H), 1.96-2.09(m, 2H), 1.82-1.92(m, 2H), 1.37(s, 18H), 1.18-1.35(m, 2H)

45 IR(cm⁻¹) 3640, 3360, 3260, 2950, 1645, 1595, 1565, 1515, 1245, 1045, 760

Example 82

50 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-phenethyl-4-piperidyl)urea



The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-amino-1-phenethylpiperidine instead of decylamine. m.p. 175-176°C

¹H-NMR(δ ppm, CDCl₃) 7.15-7.31(m, 9H), 6.78(s, 2H), 5.12(s, 1H), 5.01(s, 1H), 4.13(d, J=8Hz, 1H), 3.58-3.73(m, 1H), 2.72-2.91(m, 8H), 2.50-2.57(m, 2H), 2.05-2.16(m, 2H), 1.38(s, 18H), 1.24-1.35(m, 2H)
IR(cm⁻¹) 3640, 3340, 2950, 1640, 1590, 1565, 1435, 1235, 770, 750, 700

20

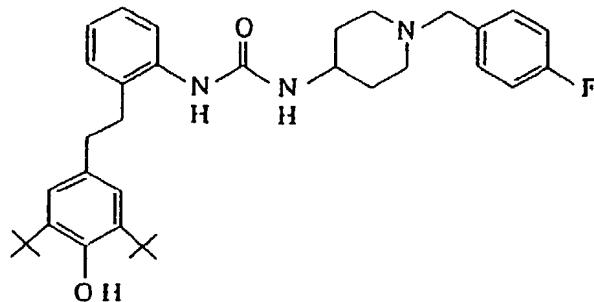
Example 83

25

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-(4-fluorobenzyl)-4-piperidyl)urea

30

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40

The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-amino-1-(4-fluorobenzyl)piperidine instead of decylamine.

m.p. 174-175°C

¹H-NMR(δ ppm, CDCl₃) 7.16-7.29(m, 6H), 6.93-7.00(m, 2H), 6.77(s, 2H), 5.11(s, 1H), 4.97(s, 1H), 4.09(d, J=8Hz, 1H), 3.57-3.71(m, 1H), 3.39(s, 2H), 2.66-2.87(m, 6H), 1.98-2.08(m, 2H), 1.82-1.90(m, 2H), 1.37(s, 18H), 1.22-1.34(m, 2H)

45

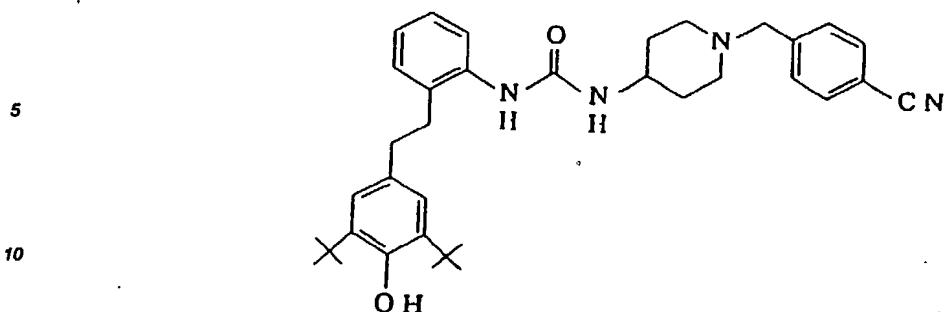
IR(cm⁻¹) 3645, 3370, 2950, 1540, 1590, 1560, 1510, 1225, 750

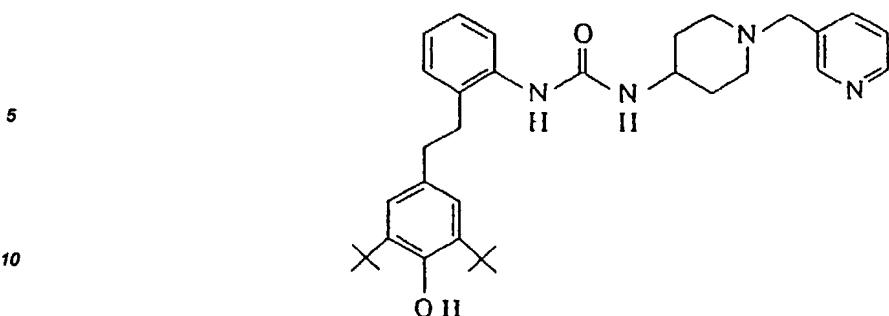
Example 84

50

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-(4-cyanobenzyl)-4-piperidyl)urea

55





15 The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-amino-1-(3-pyridylmethyl)piperidine instead of decylamine.

m.p. 156-158°C

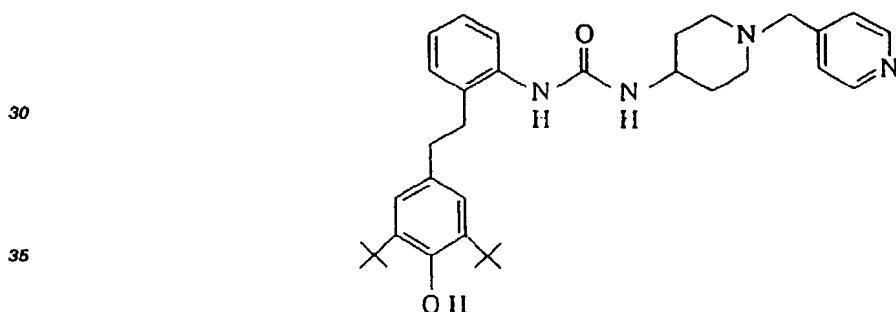
1H-NMR(δ ppm, CDCl₃) 8.46-8.52(m, 2H), 7.60(d, J=8Hz, 1H), 7.16-7.28(m, 5H), 6.77(s, 2H), 5.12(s, 1H), 5.02(s, 1H), 4.13(d, J=8Hz, 1H), 3.58-3.72(m, 1H), 3.45(s, 2H), 2.67-2.87(m, 6H), 2.03-2.12(m, 2H), 1.82-1.90(m, 2H), 1.37(s, 18H), 1.22-1.37(m, 2H)

20 IR(cm⁻¹) 3632, 3362, 2950, 1645, 1561, 1433, 1232, 759, 713

Example 87

25 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-(4-pyridylmethyl)-4-piperidyl)urea

25



40 The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-amino-1-(4-pyridylmethyl)piperidine instead of decylamine.

m.p. 156-158°C

1H-NMR(δ ppm, CDCl₃) 8.51(dd, J=4, 2Hz, 2H), 7.16-7.28(m, 6H), 6.77(s, 2H), 5.12(s, 1H), 5.00(s, 1H), 4.12(d, J=8Hz, 1H), 3.60-3.72(m, 1H), 3.44(s, 2H), 2.74-2.88(m, 4H), 2.66-2.74(m, 2H), 2.04-2.14(m, 2H), 1.83-1.92(m, 2H), 1.38(s, 18H), 1.25-1.38(m, 2H)

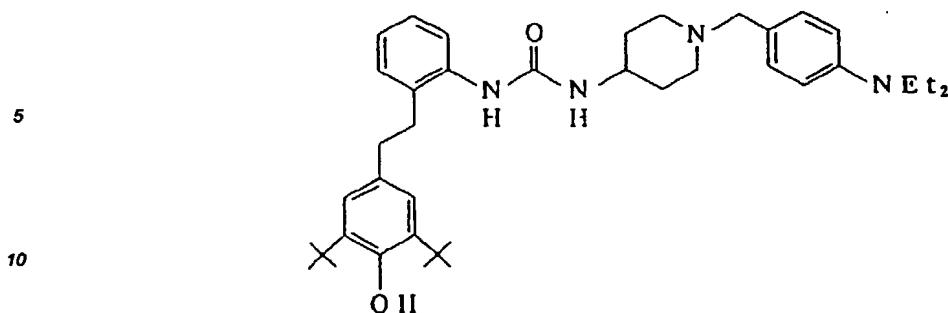
45 IR(cm⁻¹) 3630, 3292, 2948, 1620, 1560, 1435, 1237, 1109, 759

Example 88

50 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-(4-diethylaminobenzyl)-4-piperidyl)urea

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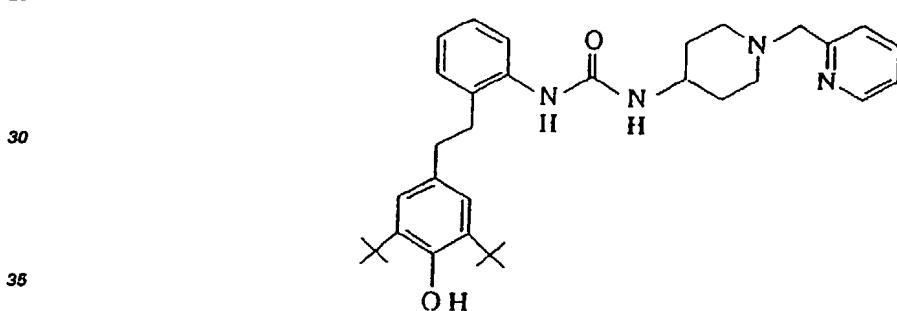


1H-NMR(δ ppm, CDCl_3) 7.16-7.27(m, 4H), 7.09(d, $J=8\text{Hz}$, 2H), 6.77(s, 2H), 6.60(d, $J=8\text{Hz}$, 2H), 5.11(s, 1H), 4.99(s, 1H), 4.12(bd, $J=7\text{Hz}$, 1H), 3.58-3.70(m, 1H), 3.28-3.40(m, 6H), 2.73-2.86(m, 6H), 1.98-2.08(m, 2H), 1.82-1.89(m, 2H), 1.37(s, 18H), 1.25-1.37(m, 2H), 1.14(t, $J=7\text{Hz}$, 6H)

20 IR(cm^{-1}) 3630, 3410, 2950, 1641, 1553, 1520, 1232, 758

Example 89

25 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[1-(2-pyridylmethyl)-4-piperidyl]urea



The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-amino-1-(2-pyridylmethyl)piperidine instead of decylamine.

40 m.p. 106-109°C

1H-NMR(δ ppm, CDCl_3) 8.54(d, $J=4\text{Hz}$, 1H), 7.58-7.65(m, 1H), 7.33(d, $J=8\text{Hz}$, 1H), 7.12-7.27(m, 6H), 6.77(s, 2H), 5.11(s, 1H), 5.01(s, 1H), 4.14(d, $J=7\text{Hz}$, 1H), 3.61-3.73(m, 1H), 3.59(s, 2H), 2.70-2.86(m, 6H), 2.12-2.21(m, 2H), 1.83-1.91(m, 2H), 1.37(s, 18H), 1.30-1.42(m, 2H)

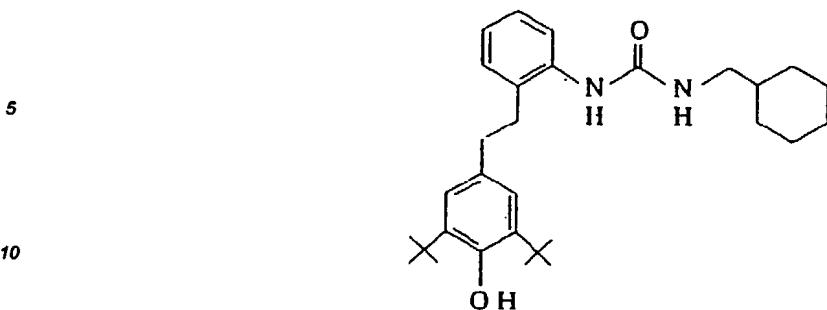
45 IR(cm^{-1}) 3630, 3330, 2948, 1639, 1589, 1543, 1436, 1233, 1121, 756

Example 90

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(cyclohexylmethyl)urea

50

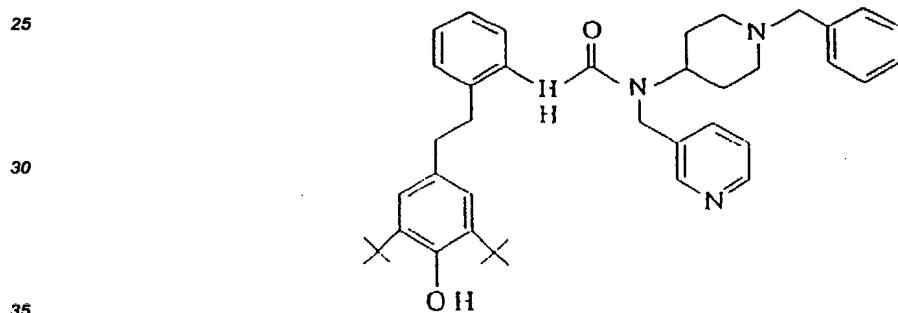
55



15 The title compound was prepared in a similar manner to that mentioned in Example 11, using aminomethylcyclohexane instead of decylamine. m.p. 208-210°C
¹H-NMR(δ ppm, CDCl₃) 7.18-7.24(m, 4H), 6.78(s, 2H), 5.11(s, 1H), 4.98(bs, 1H), 4.18-4.28(m, 1H),
2.97(t, J=6Hz, 2H), 2.74-2.90(m, 4H), 1.55-1.70(m, 5H), 1.38(s, 18H), 1.08-1.30(m, 4H), 0.78-0.90(m, 2H)
IR(cm⁻¹) 3616, 3304, 2922, 1627, 1579, 1435, 1233

20 Example 91

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-benzyl-4-piperidyl)-N'-(3-pyridylmethyl)urea



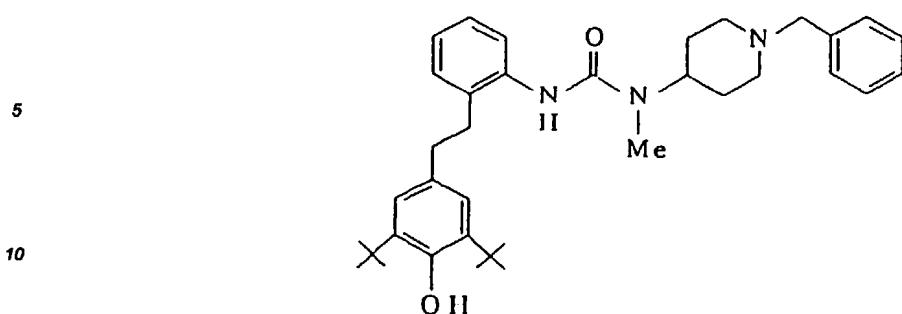
35 The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-benzyl-4-(3-pyridylmethylamino)piperidine instead of decylamine.
m.p. 127-130°C
40 ¹H-NMR(δ ppm, CDCl₃) 8.55(d, J=2Hz, 1H), 8.41(dd, J=5, 2Hz, 1H), 7.65(d, J=8Hz, 1H), 7.59(d, J=8Hz, 1H), 7.13-7.30(m, 6H), 7.18(m, 1H), 7.10(dd, J=8, 5Hz, 1H), 7.01(d, J=4Hz, 2H), 6.75(s, 2H), 5.90(bs, 1H), 5.11(s, 1H), 4.45(s, 2H), 4.22-4.33(m, 1H), 3.47(s, 2H), 2.88-2.97(m, 2H), 2.61(t, J=7Hz, 2H), 2.44(t, J=7Hz, 2H), 2.00-2.14(m, 2H), 1.60-1.86(m, 4H), 1.38(s, 18H)
IR(cm⁻¹) 3450, 3290, 1628, 1512, 1264, 1121, 1029, 742

45 Example 92

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-benzyl-4-piperidyl)-N'-methylurea

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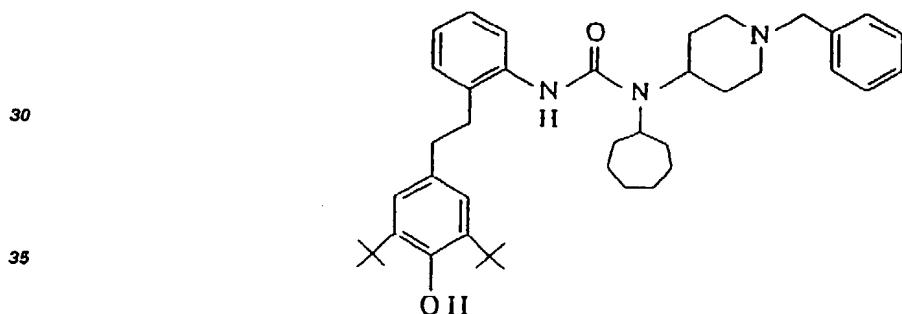
15 The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-benzyl-4-(methylamino)piperidine instead of decylamine.
m.p. 144-146°C

1H-NMR(δ ppm, CDCl₃) 7.62(d, J=8Hz, 1H), 7.10-7.30(m, 7H), 7.10(d, J=7Hz, 1H), 6.78(s, 2H), 5.62(bs, 1H), 5.08(s, 1H), 4.23(s, 1H), 3.48(s, 2H), 2.86-2.98(m, 2H), 2.81(s, 4H), 2.50(s, 3H), 1.98-2.10(m, 2H), 1.50-1.70(m, 4H), 1.35(s, 18H)

20 IR(cm⁻¹) 3328, 2954, 1632, 1512, 1196, 1041, 755, 701

Example 93

25 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-benzyl-4-piperidyl)-N'-cycloheptylurea



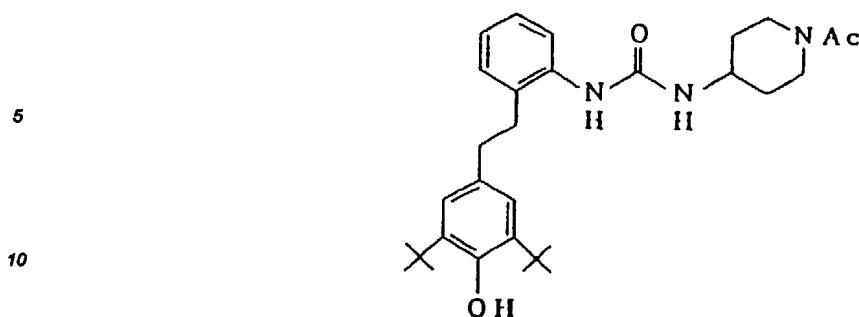
40 The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-benzyl-4-(cycloheptylamino)piperidine instead of decylamine.
m.p. 107-109°C

45 1H-NMR(δ ppm, CDCl₃) 7.72(d, J=8Hz, 1H), 7.23-7.36(m, 5H), 7.19(t, J=7Hz, 1H), 7.13(d, J=6Hz, 1H), 7.02(t, J=7Hz, 1H), 6.93(s, 2H), 6.12(bs, 1H), 5.05(s, 1H), 4.04-4.154(m, 1H), 3.49(s, 2H), 3.37-3.50(m, 1H), 2.90-3.00(m, 2H), 2.84(s, 4H), 1.97-2.10(m, 4H), 1.78-1.89(m, 4H), 1.20-1.65(m, 28H)

IR(cm⁻¹) 3476, 2922, 1662, 1528, 1454, 1236, 753

Example 94

50 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-acetyl-4-piperidyl)urea



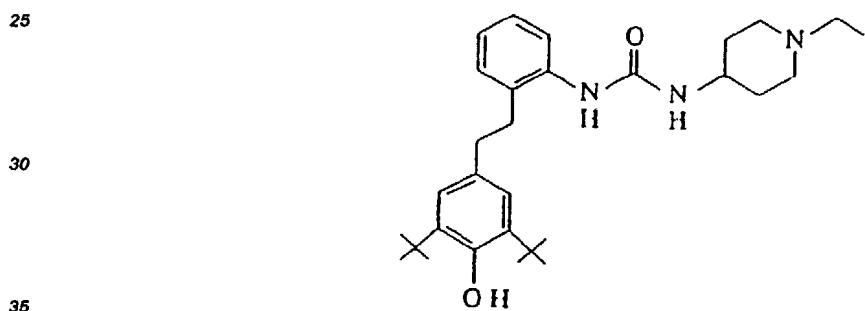
15 The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-acetyl-4-aminopiperidine instead of decylamine. m.p. 218-221°C

¹H-NMR (δ ppm, CDCl₃) 7.15-7.29(m, 4H), 6.76(s, 2H), 5.13(s, 1H), 4.93(bs, 1H), 4.43-4.52(m, 1H), 4.05-4.13(m, 1H), 3.76-3.90(m, 1H), 3.66-3.73(m, 1H), 3.04-3.14(m, 1H), 2.71-2.85(m, 4H), 2.58-2.70(m, 1H), 2.05(s, 3H), 1.95-2.06(m, 1H), 1.82-1.90(m, 1H), 1.37(s, 18H), 1.10-1.20(m, 2H)

30

Example 95

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-ethyl-4-piperidyl)urea



The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-amino-1-ethylpiperidine instead of decylamine. m.p. 182-184°C

40 ¹H-NMR(δ ppm, CDCl₃) 7.10-7.30(m, 4H), 6.77(s, 2H), 5.11(s, 1H), 5.00(bs, 1H), 4.14(bd, J=8Hz, 1H), 3.58-3.72(m, 1H), 2.70-2.90(m, 6H), 2.39(q, J=7Hz), 1.97-2.12(m, 2H), 1.85-1.97(m, 2H), 1.37(s, 18H), 1.30-1.40(m, 2H), 1.07(t, J=7Hz, 3H)
 IR(cm⁻¹) 3362, 2950, 1640, 1563, 1435, 1235

Example 96

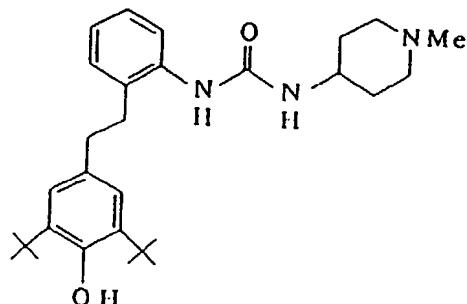
45

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-methyl-4-piperidyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-amino-1-methylpiperidine instead of decylamine. m.p. 193-195°C

¹H-NMR(δ ppm, CDCl₃) 7.15-7.25(m, 4H), 6.77(s, 2H), 5.12(s, 1H), 4.97(bs, 1H), 4.10(bd, J=8Hz, 1H), 3.58-3.70(m, 1H), 2.70-2.85(m, 6H), 2.25(s, 3H), 2.02-2.12(m, 2H), 1.84-1.93(m, 2H), 1.38(s, 18H), 1.30-1.43(m, 2H)

IR(cm⁻¹) 3360, 2944, 1639, 1562

20

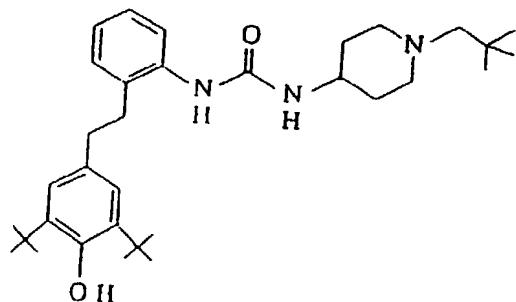
Example 97

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-(2,2-dimethylpropyl)-4-piperidyl)urea

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O H

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-amino-1-(2,2-dimethylpropyl)piperidine instead of decylamine.

¹H-NMR(δ ppm, CDCl₃) 7.18-7.26(m, 4H), 6.78(s, 2H), 5.11(s, 1H), 5.06(bs, 1H), 4.12(bd, J=8Hz, 1H), 3.53-3.65(m, 1H), 2.75-2.90(m, 4H), 2.60-2.68(m, 2H), 2.22-2.32(m, 2H), 1.98(s, 2H), 1.73-1.83(m, 2H), 1.38(s, 18H), 1.20-1.40(m, 2H), 0.81(s, 9H)

IR(cm⁻¹) 3322, 2952, 1638, 1536, 1435, 1234

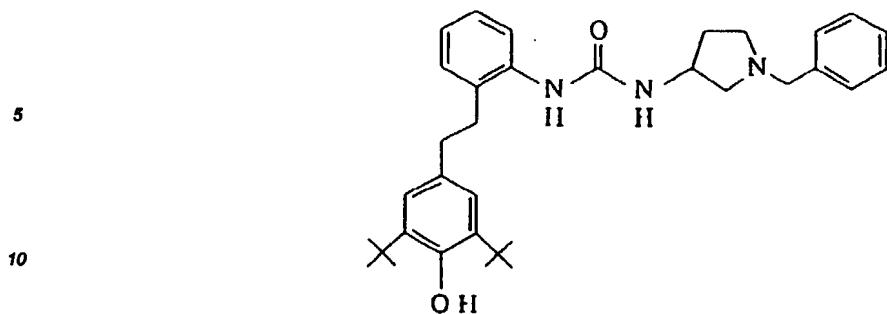
45

Example 98

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-benzyl-3-pyrrolidinyl)urea

50

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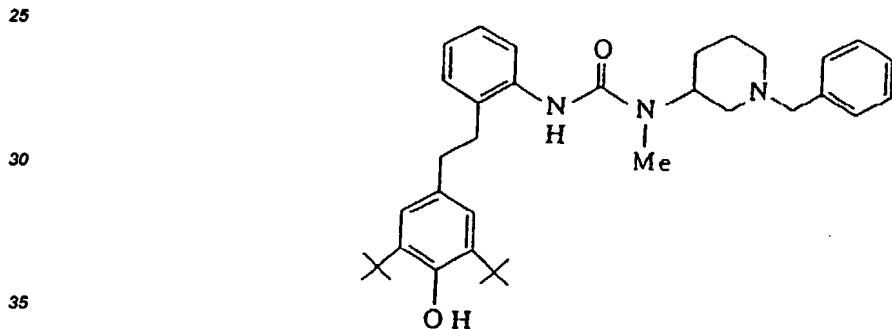
15 The title compound was prepared in a similar manner to that mentioned in Example 11, using 3-amino-1-benzylpyrrolidine instead of decylamine.

1H-NMR(δ ppm, CDCl₃) 7.10-7.30(m, 9H), 6.78(s, 2H), 5.37(bs, 1H), 5.10(s, 1H), 4.71(bd, J=8Hz, 1H), 4.23-4.34(m, 1H), 3.55(d, J=13Hz, 1H), 3.50(d, J=13Hz, 1H), 2.70-2.81(m, 6H), 2.49(d, J=4Hz, 2H), 2.14-2.36(m, 2H), 1.37(s, 18H)

20 IR(cm⁻¹) 3634, 3304, 2954, 1638, 1559, 1436, 1234, 749, 699

25 Example 99

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-benzyl-3-piperidyl)-N'-methylurea



40 The title compound was prepared in a similar manner to that mentioned in Example 11, using 3-amino-1-benzylpiperazine instead of decylamine.

1H-NMR(δ ppm, CDCl₃) 7.59(d, J=8Hz, 1H), 7.15-7.40(m, 7H), 7.08(t, J=7Hz, 1H), 6.79(s, 2H), 5.72(bs, 1H), 5.06(s, 1H), 4.22-4.34(m, 1H), 3.48(s, 2H), 2.70-2.80(m, 6H), 2.58(s, 3H), 1.60-1.90(m, 4H), 1.30-1.46(m, 2H), 1.35(s, 18H)

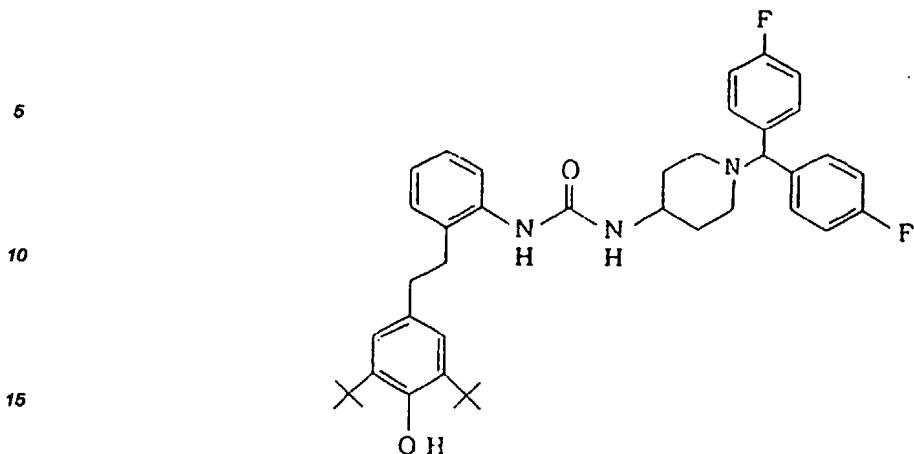
IR(cm⁻¹) 3630, 3422, 2940, 1639, 1520, 1485, 1452, 1312, 1249, 1122, 752, 699

45 Example 100

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[1-[bis(4-fluorophenyl)methyl]-4-piperidyl]urea

50

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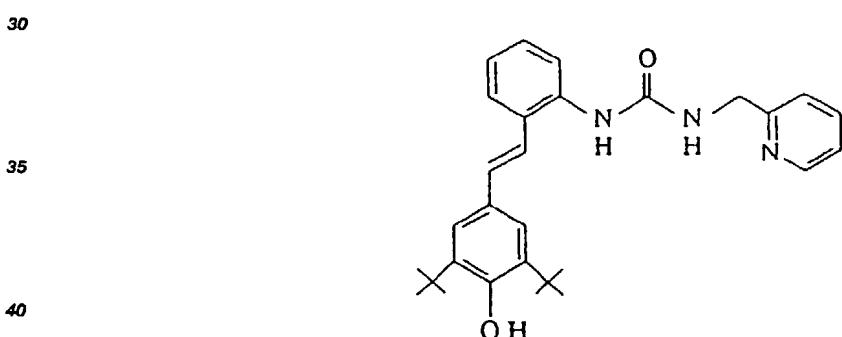


The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-amino-1-[bis(4-fluorophenyl)methyl]piperidine instead of decylamine.

20 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.65-7.80(m, 4H), 7.15-7.30(m, 4H), 7.12(t, $J=7\text{Hz}$, 2H), 6.84(d, $J=9\text{Hz}$, 2H),
6.77(s, 2H), 5.11(s, 1H), 5.01(bs, 1H), 4.13(t, $J=7\text{Hz}$, 2H), 3.75-3.95(m, 3H), 2.91-3.03(m, 2H), 2.75-2.90(m, 4H), 1.92-2.03(m, 2H), 1.25-1.40(m, 2H), 1.37(s, 18H)
25 $\text{IR}(\text{cm}^{-1})$ 3314, 2948, 1638, 1602, 1544, 1303, 1226, 1153, 768

25 Example 101

N-[2-(3,5-di-tert-butyl-4-hydroxystyryl)phenyl]-N'-(2-pyridylmethyl)urea



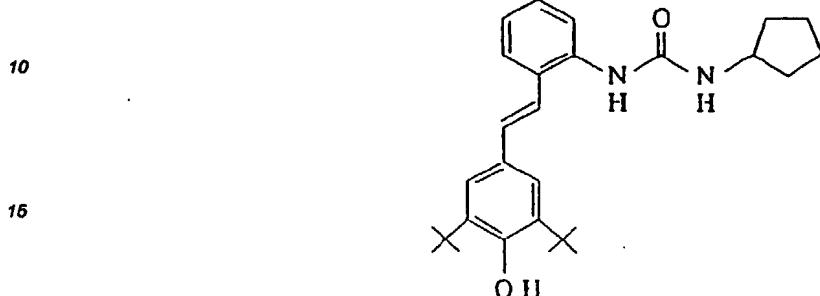
(1) To a solution of 4-(2-aminostyryl)-2,6-di-tert-butylphenol (4.85 g, 15.0 mmol) and diisopropylamine (1.72 g, 17.0 mmol) in methylene chloride (30 ml) was added dropwise under ice-cooling phenyl chloroformate (2.51 g, 16.0 mmol). The mixture was stirred for 7 hrs, while returning slowly to room temperature. To the mixture was added diisopropylamine (0.51 g, 5.0 mmol) and added dropwise under ice-cooling diisopropylamine (0.51 g, 5.0 mmol). This mixture was stirred for 3 hrs, while returning slowly to room temperature. The reaction solution was washed with water and a saturated NaCl solution, dried over MgSO_4 and concentrated. Purification of the residue by a silica gel column chromatography gave N-[2-(3,5-di-tert-butyl-4-hydroxystyryl)phenyl]phenyl carbamate (6.65 g, 99%) as a viscous oil.

45 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.91(b, 1H), 6.90-7.53(m, 13H), 5.35(s, 1H), 1.49(s, 18H)
(2) A solution of N-[2-(3,5-di-tert-butyl-4-hydroxystyryl)phenyl]phenyl carbamate (1.00 g, 2.25 mmol) and 2-(aminomethyl)pyridine (0.27 g, 2.50 mmol) in xylene (5 ml) was stirred at 80-100°C for 3 hrs. After distilling off the solvent, purification of the residue by a silica gel column chromatography afforded N-[2-(3,5-di-tert-butyl-4-hydroxystyryl)phenyl]-N'-(2-pyridylmethyl)urea (0.54 g, 71%) as crystals. m.p. 207-210°C

55 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 8.37(d, $J=4\text{Hz}$, 1H), 7.59(dd, $J=8, 2\text{Hz}$, 1H), 7.51(d, $J=7\text{Hz}$, 1H), 7.43-7.50(m, 1H), 7.31(s, 2H), 7.16-7.28(m, 3H), 7.17(d, $J=16\text{Hz}$, 1H), 7.02-7.07(m, 1H), 6.99(d, $J=16\text{Hz}$, 1H), 6.68-6.91(m, 1H), 5.79-5.87(m, 1H), 5.32(s, 1H), 4.51(d, $J=5\text{Hz}$, 2H), 1.45(s, 18H)

IR(cm⁻¹) 3350, 3270, 2960, 1640, 1560, 1475, 1440, 1235, 1010, 755, 740

Example 102

5 N-[2-(3,5-di-tert-butyl-4-hydroxystyryl)phenyl]-N'-cycloheptylurea

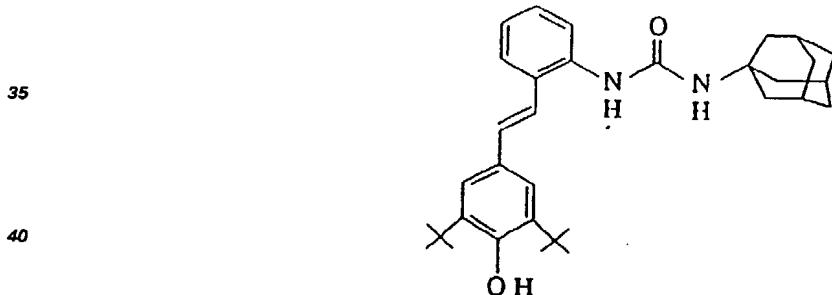
20 The title compound was prepared in a similar manner to that mentioned in Example 101, using cycloheptylamine instead of 2-(aminomethyl)pyridine.

m.p. 203-206°C

1H-NMR(δ ppm, CDCl₃) 7.61(d, J=8Hz, 1H), 7.38(d, J=8Hz, 1H), 7.33(s, 2H), 7.18-7.28(m, 2H), 7.06(d, J=16Hz, 1H), 7.00(d, J=16Hz, 1H), 6.05(s, 1H), 5.33(s, 1H), 4.48-4.55(m, 1H), 4.04-4.16(m, 1H), 1.88-2.00(m, 2H), 1.48-1.62(m, 4H), 1.47(s, 18H), 1.22-1.37(m, 2H)

IR(cm⁻¹) 3630, 3310, 2950, 1630, 1560, 1440, 1235, 960, 745

Example 103

30 N-[2-(3,5-di-tert-butyl-4-hydroxystyryl)phenyl]-N'-adamantylurea

45 The title compound was prepared in a similar manner to that mentioned in Example 101, using 1-adamantanamine instead of 2-(aminomethyl)pyridine.

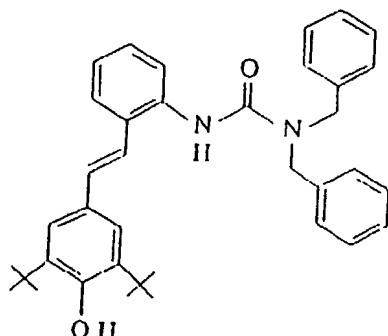
m.p. 205-211°C

1H-NMR(δ ppm, CDCl₃) 7.66(dd, J=7, 2Hz, 1H), 7.34(s, 2H), 7.29-7.36(m, 1H), 7.15-7.29(m, 2H), 7.06(d, J=16Hz, 1H), 7.00(d, J=16Hz, 1H), 5.90(s, 1H), 5.33(s, 1H), 4.34(s, 1H), 1.82-2.06(m, 9H), 1.52-1.67(m, 6H), 1.47(s, 18H)

50 IR(cm⁻¹) 3630, 3330, 2900, 1640, 1560, 1525, 1235, 740,

Example 104

55 N-[2-(3,5-di-tert-butyl-4-hydroxystyryl)phenyl]-N',N'-dibenzylurea



The title compound was prepared in a similar manner to that mentioned in Example 101, using N,N-dibenzylamine instead of 2-(aminomethyl)pyridine.

m.p. 175-178°C

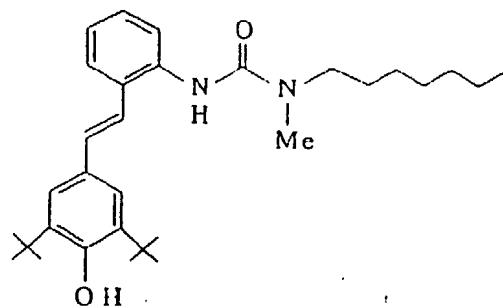
$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.79(dd, $J=8, 1\text{Hz}$, 1H), 7.36(dd, $J=8, 1\text{Hz}$, 1H), 7.02-7.30(m, 13H), 7.02-7.08(m, 1H), 6.78(d, $J=16\text{Hz}$, 1H), 6.65(d, $J=16\text{Hz}$, 1H), 5.31(s, 1H), 4.60(s, 4H), 1.47(s, 18H)

20 IR(cm^{-1}) 3420, 3390, 2940, 1660, 1580, 1520, 1450, 1435, 1230, 960, 755

Example 105

N-[2-(3,5-di-tert-butyl-4-hydroxystyryl)phenyl]-N'-methyl-N'-heptylurea

25



40 The title compound was prepared in a similar manner to that mentioned in Example 101, using N-methyl-heptylamine instead of 2-(aminomethyl)pyridine.

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.81(d, $J=8\text{Hz}$, 1H), 7.44(d, $J=8\text{Hz}$, 1H), 7.32(s, 2H), 7.22-7.27(m, 1H), 7.05-7.10(m, 1H), 7.00(d, $J=16\text{Hz}$, 1H), 6.93(d, $J=16\text{Hz}$, 1H), 6.36(s, 1H), 5.32(s, 1H), 3.34(d, $J=8\text{Hz}$, 2H), 3.02(s, 3H), 1.54-1.65(m, 2H), 1.47(s, 18H), 1.16-1.32(m, 8H), 0.84(t, $J=7\text{Hz}$, 3H)

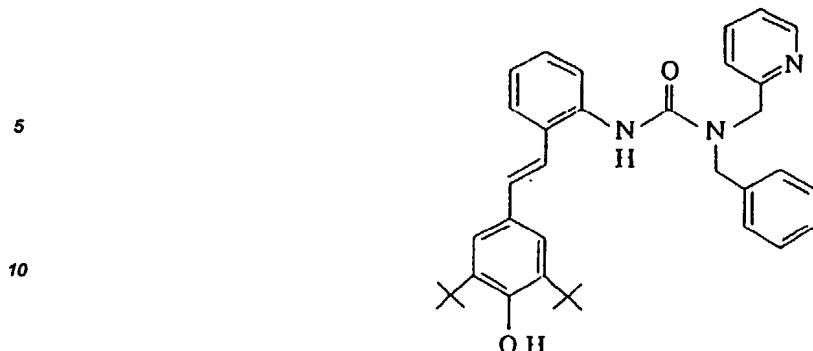
45 IR(cm^{-1}) 3640, 3450, 3300, 2960, 2930, 1640, 1580, 1520, 1485, 1440, 1240, 1155, 960, 750

Example 106

N-[2-(3,5-di-tert-butyl-4-hydroxystyryl)phenyl]-N'-benzyl-N'-(2-pyridylmethyl)urea

50

55



The title compound was prepared in a similar manner to that mentioned in Example 101, using 7-amino-3,9-dimethyl-3,9-diazabicyclo[3.3.1]nonane instead of 2-(aminomethyl)pyridine.

40 m.p. 188-191°C

¹H-NMR(δ ppm, CDCl₃) 8.78(d, J=10Hz, 1H), 7.64(dd, J=7, 2Hz, 1H), 7.30-7.35(m, 3H), 7.13-7.27(m, 2H), 7.13(d, J=2Hz, 1H), 7.02(d, J=2Hz, 1H), 5.93(s, 1H), 5.35(s, 1H), 4.22-4.33(m, 1H), 2.66-2.72(m, 2H), 2.41(s, 3H), 2.22-2.40(m, 6H), 1.48(s, 3H), 1.47(s, 18H), 1.28-1.38(m, 2H)

IR(cm⁻¹) 3410, 2940, 1630, 1600, 1510, 1440, 1390, 1265, 1185, 965, 760

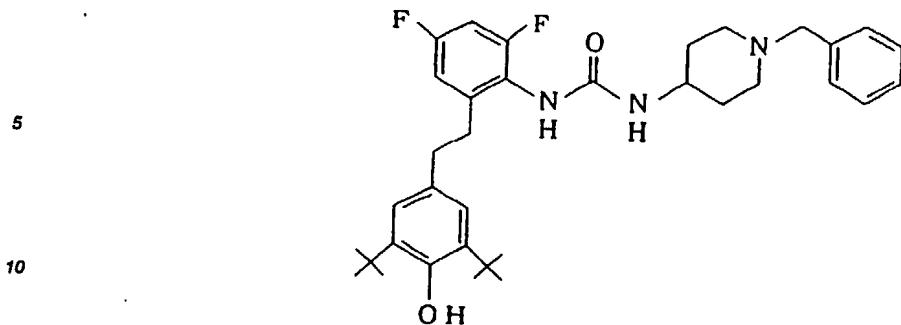
45

Example 108

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]-N'-(1-benzyl-4-piperidyl)urea

50

55



15 (1) To a solution of 4-(2-amino-3,5-difluorophenethyl)-2,6-di-tert-butylphenol (1.37 g, 3.8 mmol) and diisopropylamine (0.50 g, 4.9 mmol) in methylene chloride (20 ml) was added dropwise under ice-cooling phenyl chloroformate (0.66 g, 4.2 mmol) and the mixture was stirred for 3 hrs, while returning slowly to room temperature. Diisopropylamine (0.19 g, 1.9 mmol) was further added and phenyl chloroformate (0.30 g, 1.9 mmol) was added dropwise under ice-cooling. The mixture was stirred for 3 hrs while returning slowly to room temperature. The reaction solution was washed with water and a saturated NaCl solution, dried over MgSO₄ and concentrated. Purification of the residue by silica gel column chromatography gave N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]phenyl carbamate (1.82 g, 99%) as oil.

20 ¹H-NMR(δ ppm, CDCl₃) 7.04-7.42(m, 5H), 6.67-6.85(m, 4H), 5.16(s, 1H), 4.94(s, 1H), 2.76-3.02(m, 4H), 1.37(s, 18H)

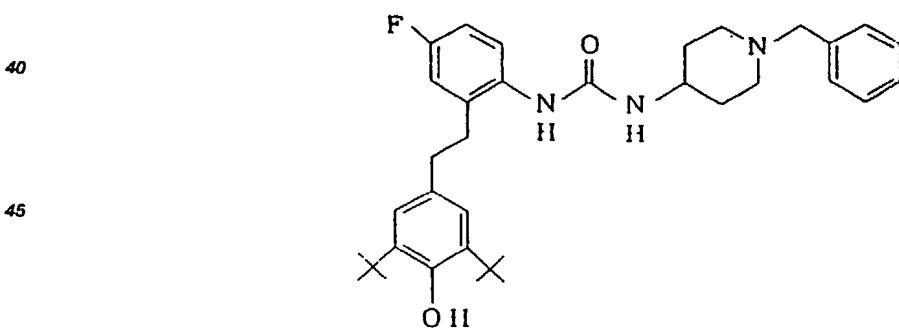
25 (2) A solution of N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]phenyl carbamate (1.82 g, 3.8 mmol) and 4-amino-1-benzylpyridine (0.72 g, 3.8 mmol) in toluene (10 ml) was stirred at 100-120°C for 2 hrs. After distilling off the solvent, purification of the residue by a silica gel column chromatography afforded N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]-N'-(1-benzyl-4-piperidyl)urea (1.39 g, 64%) as a noncrystalline solid.

30 ¹H-NMR(δ ppm, CDCl₃) 7.20-7.30(m, 5H), 6.65-6.80(m, 4H), 5.12(s, 1H), 4.79(bs, 1H), 4.14(bd, J=8Hz, 1H), 3.54-3.66(m, 1H), 3.44(s, 2H), 2.84(d, J=7Hz, 2H), 2.70-2.79(m, 4H), 1.98-2.10(m, 2H), 1.80-1.92(m, 2H), 1.30-1.40(m, 20H)

IR(cm⁻¹) 3638, 3316, 2952, 1639, 1562, 1494, 1436, 1235, 1122

Example 109

35 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4-fluorophenyl]-N'-(1-benzyl-4-piperidyl)urea



50 The title compound was prepared in a similar manner to that mentioned in Example 108, using 4-(2-amino-5-fluorophenethyl)-2,6-di-tert-butylphenol instead of 4-(2-amino-3,5-difluorophenethyl)-2,6-di-tert-butylphenol.

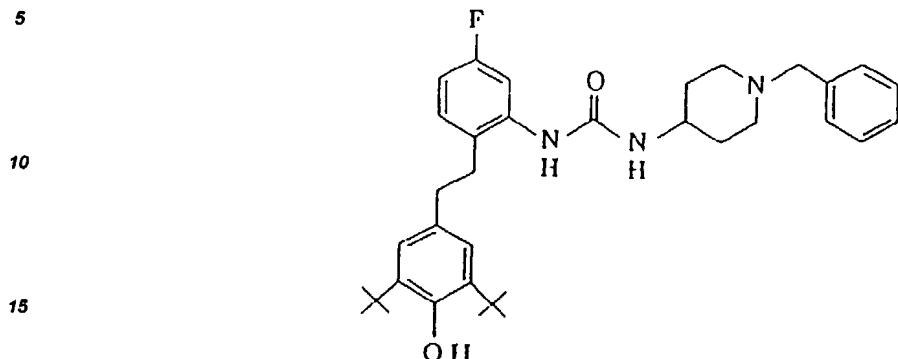
55 m.p. 108-109°C
¹H-NMR(δ ppm, CDCl₃) 7.21-7.31(m, 5H), 7.16(dd, J=9, 5Hz, 1H), 6.87-6.98(m, 2H), 6.77(s, 2H), 5.12(s, 1H), 4.86(s, 1H), 3.99(d, J=8Hz, 1H), 3.55-3.70(m, 1H), 3.44(s, 1H), 2.70-2.85(m, 6H), 2.05(t, J=11Hz, 2H), 1.85(d, J=10Hz, 2H), 1.38(s, 18H), 1.25-1.35(m, 2H)

IR(cm⁻¹) 3636, 3280, 1634, 1561, 1495, 1435, 1234, 1213, 1120, 739, 699

Example 110

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-5-fluorophenyl]-N'-(1-benzyl-4-piperidyl)urea

5



10

15

20

25

The title compound was prepared in a similar manner to that mentioned in Example 108, using 4-(2-amino-4-fluorophenethyl)-2,6-di-tert-butylphenol instead of 4-(2-amino-3,5-difluorophenethyl)-2,6-di-tert-butylphenol.

m.p. 118-119°C

¹H-NMR(δ ppm, CDCl₃) 7.20-7.32(m, 5H), 7.13-7.20(m, 2H), 6.84(dt, J=3, 8Hz, 1H), 6.78(s, 2H), 5.13(s, 1H), 5.01(s, 1H), 4.02(d, J=8Hz, 1H), 3.46-3.63(m, 1H), 3.46(s, 2H), 2.77(bs, 6H), 2.06(t, J=11Hz, 2H), 1.86(d, J=11Hz, 2H), 1.38(s, 18H), 1.30-1.40(m, 2H)

IR(cm⁻¹) 3630, 3350, 1640, 1602, 1563, 1434, 1233, 738, 700

Example 111

30 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4-methoxyphenyl]-N'-(1-benzyl-4-piperidyl)urea

35

40

45

The title compound was prepared in a similar manner to that mentioned in Example 108, using 4-(2-amino-5-methoxyphenethyl)-2,6-di-tert-butylphenol instead of 4-(2-amino-3,5-difluorophenethyl)-2,6-di-tert-butylphenol.

m.p. 174-175°C

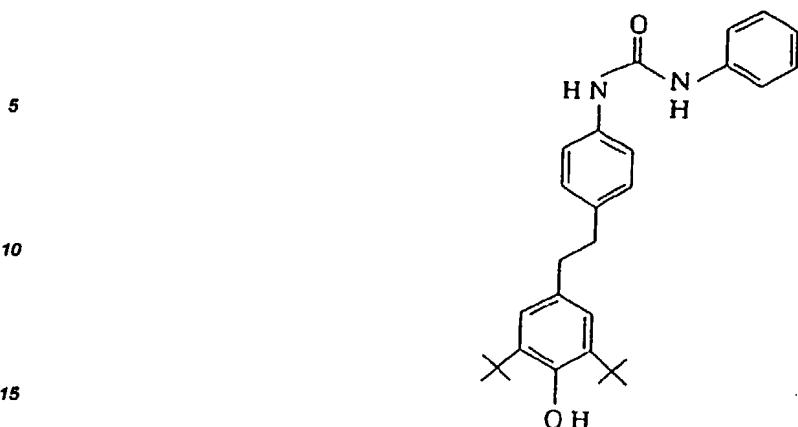
¹H-NMR(δ ppm, CDCl₃) 7.20-7.30(m, 5H), 7.00-7.07(m, 1H), 6.78(s, 2H), 6.70-6.75(m, 2H), 5.09(s, 1H), 4.91(s, 1H), 4.05(d, J=8Hz, 1H), 3.79(s, 3H), 3.60-3.65(m, 1H), 3.43(s, 2H), 2.70-2.80(m, 6H), 2.05(t, J=11Hz, 2H), 1.85(d, J=11Hz, 2H), 1.38(s, 18H), 1.20-1.40(m, 2H)

IR(cm⁻¹) 3630, 3312, 1634, 1561, 1501, 1436, 1282, 1231, 1055, 880, 750, 710

Example 112

55

N-[4-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]3-N'-phenylurea

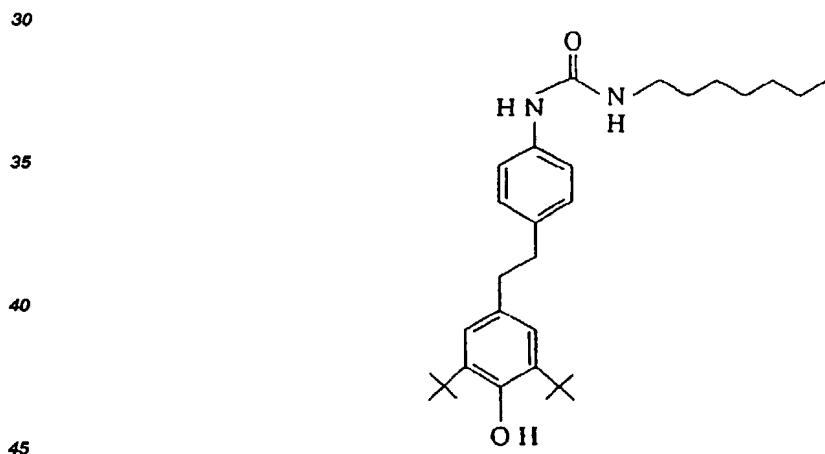


20 The title compound was prepared in a similar manner to that mentioned in Example 1, using 4-(4-aminophenethyl)-2,6-di-tert-butylphenol instead of 4-(2-aminophenethyl)-2,6-di-tert-butylphenol and using benzoic acid instead of 4-hexyloxybenzoic acid. m.p. 206-207°C

25 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.22-7.38(m, 6H), 7.18(d, $J=9\text{Hz}$, 2H), 7.08-7.14(m, 1H), 6.55(bs, 1H), 6.47(bs, 1H), 2.77-2.92(m, 4H), 1.43(s, 18H)
 $\text{IR(cm}^{-1}\text{)} 3640, 3330, 2960, 1655, 1605, 1565, 1440, 1320, 1240, 760, 695$

25 Example 113

N-[4-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-heptylurea

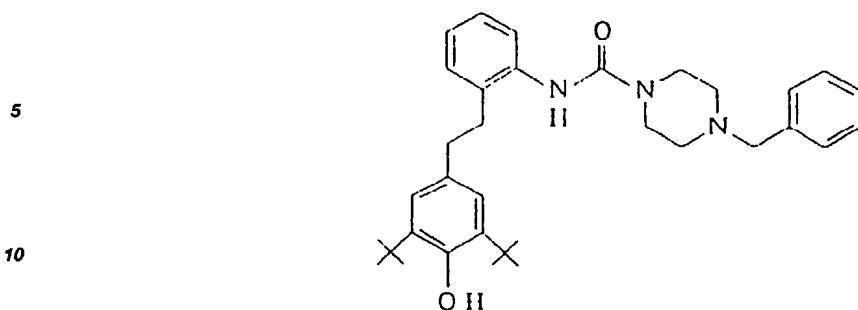


50 The title compound was prepared in a similar manner to that mentioned in Example 1, using 4-(4-aminophenethyl)-2,6-di-tert-butylphenol instead of 4-(2-aminophenethyl)-2,6-di-tert-butylphenol and n-octanoic acid instead of 4-hexyloxybenzoic acid. m.p. 151-152°C

55 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.13-7.21(m, 4H), 6.95(s, 2H), 6.22(bs, 1H), 5.06(s, 1H), 4.73(bt, $J=5\text{Hz}$, 1H), 3.23(dt, $J=5, 7\text{Hz}$, 2H), 2.75-2.90(m, 42H), 1.45-1.54(m, 2H), 1.42(s, 18H), 1.21-1.36(m, 8H), 0.88(t, $J=7\text{Hz}$, 3H)
 $\text{IR(cm}^{-1}\text{)} 3630, 3120, 2960, 2930, 2860, 1645, 1605, 1575, 1520, 1440, 1235$

55 Example 114

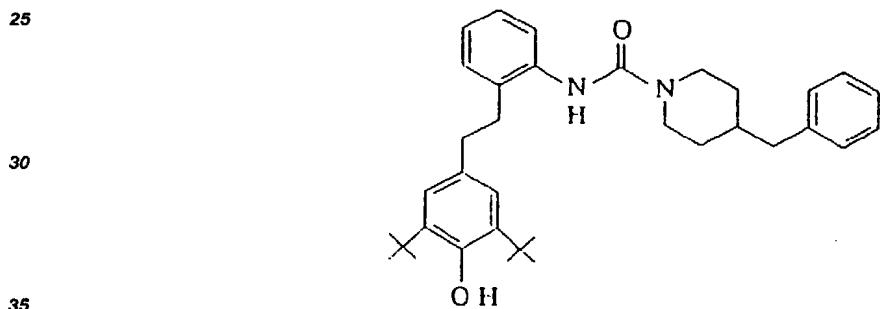
1-Benzyl-4-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]piperazine



15 The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-benzylpiperazine instead of decylamine. m.p. 70-72°C
 1H-NMR(δ ppm, CDCl_3) 7.49-7.51(m, 1H), 7.09-7.33(m, 8H), 6.78(s, 2H), 5.61(s, 1H), 5.06(s, 1H),
 3.50(s, 2H), 3.22(t, $J=5\text{Hz}$, 4H), 2.80(s, 4H), 2.39(t, $J=5\text{Hz}$, 4H), 1.33(s, 18H)
 IR(cm^{-1}) 3636, 3310, 2952, 1635, 1516, 1435, 1234, 1001, 754

20 Example 115

4-Benzyl-1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]piperidine



35 The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-benzylpiperidine instead of decylamine.

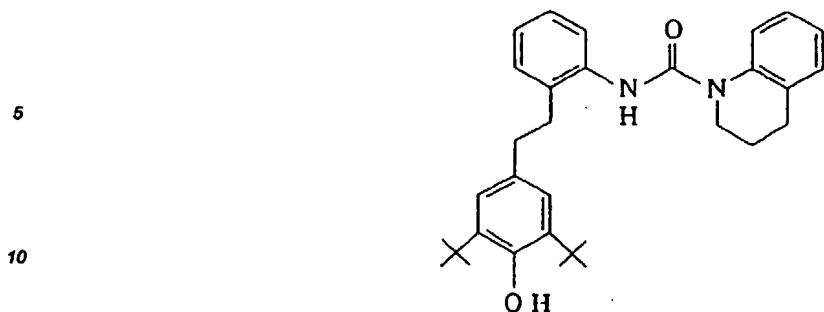
40 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.52(d, $J=8\text{Hz}$, 1H), 7.06-7.32(m, 8H), 6.79(s, 2H), 5.67 (s, 1H), 5.06(s, 1H),
 3.68-3.76 (m, 2H), 2.81(s, 4H), 2.62-2.72(m, 2H), 2.53(t, $J=7\text{Hz}$, 4H), 1.50-1.73(m, 3H), 1.35(s, 18H), 1.10-
 1.23(m, 2H)
 IR(cm^{-1}) 3645, 3440, 3330, 2960, 2925, 1645, 1525, 1455, 1440, 1250, 755, 705

45 Example 116

45 1-[N-2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-1,2,3,4-tetrahydroquinoline

50

55



15 The title compound was prepared in a similar manner to that mentioned in Example 11, using 1,2,3,4-tetrahydroisoquinoline instead of decylamine.

1H-NMR(δ ppm, CDCl₃) 7.82(d, J=7Hz, 1H), 7.36(d, J=7Hz, 1H), 7.13-7.21(m, 2H), 7.16(d, J=7Hz, 1H), 6.99-7.09(m, 3H), 6.89(bs, 1H), 6.82(s, 2H), 5.06(s, 1H), 3.80(t, J=6Hz, 2H), 2.78(t, J=6Hz, 2H), 2.69(s, 4H), 1.98(m, 2H), 1.39(s, 18H)

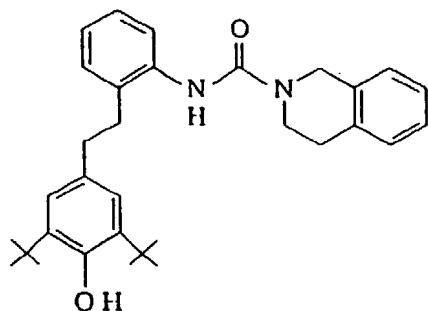
IR(cm⁻¹) 3630, 3434, 2946, 1671, 1524, 1492, 1435, 1304, 1236, 753

20

Example 117

25 2-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-1,2,3,4-tetrahydroisoquinoline

30



35 The title compound was prepared in a similar manner to that mentioned in Example 11, using 1,2,3,4-tetrahydroisoquinoline instead of decylamine. m.p. 148-150°C

40 1H-NMR(δ ppm, CDCl₃) 7.55(d, J=8Hz, 1H), 7.10-7.26(m, 7H), 6.83(s, 1H), 5.73(bs, 1H), 5.10(s, 1H), 4.52(s, 2H), 3.44(t, J=6Hz, 2H), 2.86(t, J=6Hz, 2H), 2.84(s, 4H), 1.36(s, 18H)

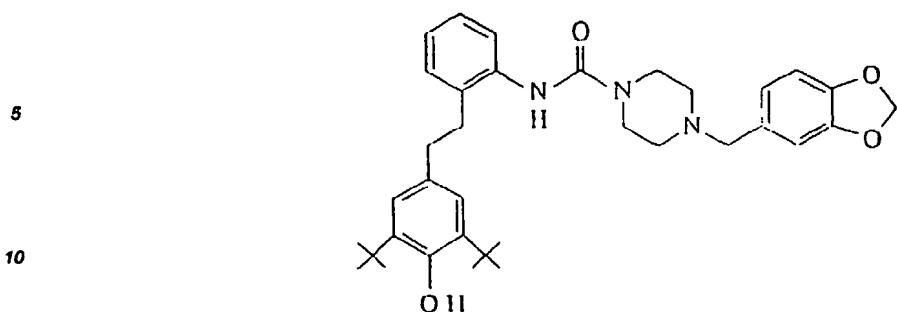
IR(cm⁻¹) 3628, 3312, 1630, 1515, 1459, 1437, 1373, 1231, 747

45

Example 118

50 1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-4-(3,4-methylenedioxybenzyl)piperazine

55



15 The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-(3,4-me-
thylenedioxybenzyl)piperazine instead of decylamine.

m.p. 149-151°C

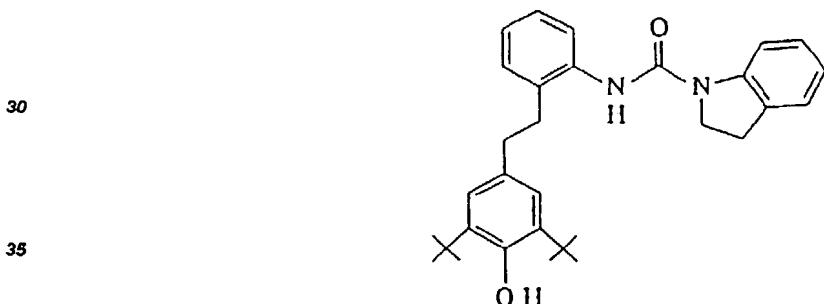
1H-NMR(δ ppm, CDCl₃) 7.50(d, J=7Hz, 1H), 7.18-7.23(m, 2H), 7.11(dd, J=7, 7Hz, 1H), 6.83(s, 1H), 6.70-
6.76(m, 2H), 5.95(s, 2H), 5.61(bs, 1H), 5.06(s, 1H), 3.40(s, 2H), 3.22(t, J=5Hz, 4H), 2.80(s, 4H), 2.36(t, J=5Hz,
4H), 1.34(s, 18H)

20 IR(cm⁻¹) 3626, 3302, 2956, 1632, 1504, 1491, 1438, 1247, 1040, 999, 759

Example 119

1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]indoline

25



40 The title compound was prepared in a similar manner to that mentioned in Example 11, using indoline in-
stead of decylamine.

1H-NMR(δ ppm, CDCl₃) 7.91(d, J=8Hz, 1H), 7.61(d, J=8Hz, 1H), 7.10-7.30(m, 2H), 6.91(dd, J=8, 8Hz,
2H), 6.81(d, J=8Hz, 2H), 6.78(s, 2H), 5.65(bs, 1H), 5.10(s, 1H), 3.57(t, J=8Hz, 2H), 3.14(t, J=8Hz, 2H), 2.86(s,
4H), 1.35(s, 18H)

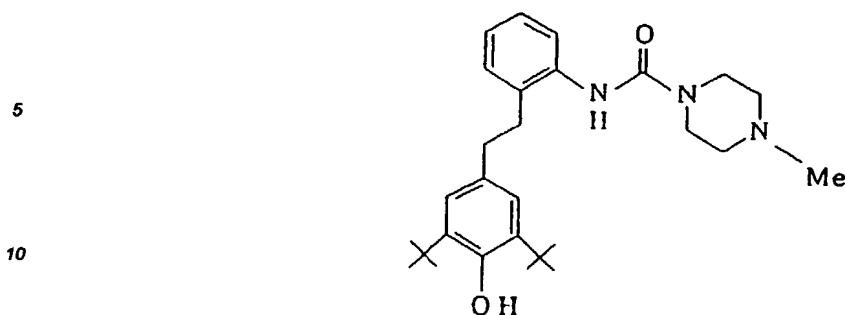
45 IR(cm⁻¹) 3622, 3272, 2952, 1654, 1594, 1507, 1485, 1448, 1347, 1234, 753

Example 120

1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-4-methylpiperazine

50

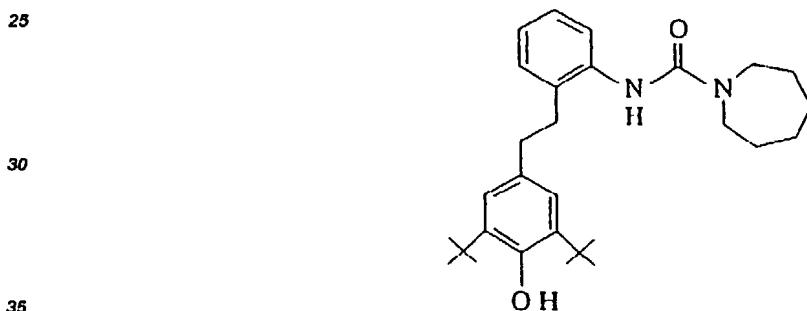
55



The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-methylpiperazine instead of decylamine. m.p. 134-137°C
 1H-NMR(δ ppm, CDCl₃) 7.47(d, J=8Hz, 1H), 7.17-7.26(m, 2H), 7.12(ddd, J=7, 7, 2Hz, 1H), 6.79(s, 2H),
 5.56(s, 1H), 5.10(s, 1H), 3.25(t, J=5Hz, 4H), 2.82(s, 4H), 2.35(t, J=5Hz, 4H), 2.29(s, 3H), 1.37(s, 18H)
 IR(cm⁻¹) 3632, 3440, 2940, 1636, 1511, 1437, 1002, 750

20 Example 121

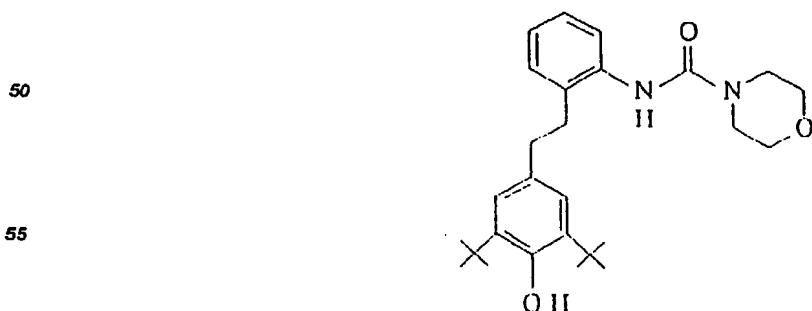
1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]perhydroazepine



The title compound was prepared in a similar manner to that mentioned in Example 11, using hexamethylenetetramine instead of decylamine. m.p. 136-138°C
 1H-NMR(δ ppm, CDCl₃) 7.67(dd, J=7, 2Hz, 1H), 7.17-7.24(m, 2H), 7.08(ddd, J=7, 7, 2Hz, 1H), 6.82(s, 2H), 5.78(s, 1H), 5.08(s, 1H), 3.26-3.34(m, 4H), 2.82(bs, 1H), 1.66-1.74(m, 4H), 1.52-1.59(m, 4H), 1.37(s, 18H)
 IR(cm⁻¹) 3460, 1660, 1587, 1525, 1453, 1436, 755

Example 122

45 4-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]morpholine



The title compound was prepared in a similar manner to that mentioned in Example 11, using morpholine instead of decylamine. m.p. 186-189°C

¹H-NMR(δ ppm, CDCl₃) 7.47(dd, J=8, 2Hz, 1H), 7.19-7.27(m, 2H), 7.14(dd, J=7, 7, 2Hz, 1H), 6.78(s, 2H), 5.52(s, 1H), 5.09(s, 1H), 3.64(t, J=5Hz, 4H), 3.19(t, J=5Hz, 4H), 2.82(s, 4H), 1.36(s, 18H)
⁵ IR(cm⁻¹) 3644, 3420, 3290, 2956, 1631, 1525, 1435, 1262, 1118, 756

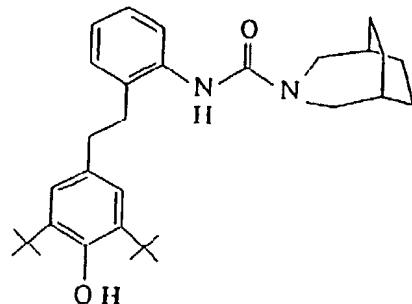
Example 123

3-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-3-azabicyclo[3.2.2]nonane

¹⁰

¹⁵

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³⁰

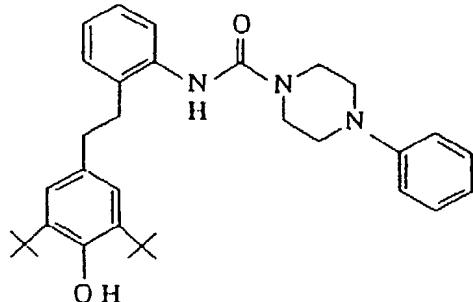
Example 124

1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-4-phenylpiperazine

³⁵

⁴⁰

⁴⁵



⁵⁰

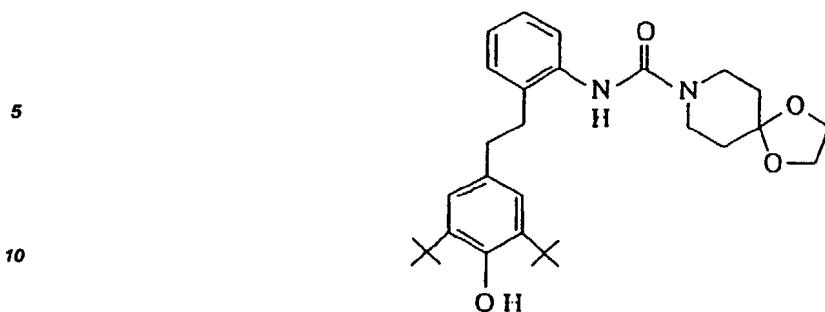
The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-phenylpiperazine instead of decylamine. m.p. 155-156°C

⁵⁵ ¹H-NMR(δ ppm, CDCl₃) 7.11-7.48(m, 6H), 6.88-6.92(m, 1H), 6.89(d, J=8Hz, 2H), 6.79(s, 2H), 5.61(t, J=5Hz, 4H), 3.12(t, J=5Hz, 4H), 2.83(s, 4H), 1.37(s, 18H)
IR(cm⁻¹) 3584, 3372, 2960, 1639, 1601, 1505, 1435, 1234, 999, 753

⁵⁵

Example 125

8-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-1,4-dioxa-8-azaspiro[4.5]decane

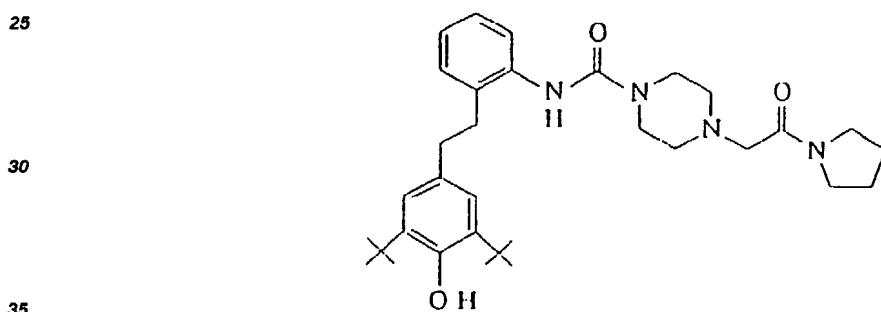


15 The title compound was prepared in a similar manner to that mentioned in Example 11, using 1,4-dioxa-8-azaspiro[4.5]decane instead of decylamine. m.p. 163-164°C

1H-NMR(δ ppm, CDCl₃) 7.45(d, J=7Hz, 1H), 7.17-7.26(m, 2H), 7.12(dd, J=7, 7Hz, 1H), 6.78(s, 2H), 5.59(bs, 1H), 5.09(s, 1H), 3.96(s, 4H), 3.30(t, J=6Hz, 4H), 2.82(s, 4H), 1.65(t, J=6Hz, 4H), 1.36(s, 18H)
IR(cm⁻¹) 3430, 3300, 2955, 1645, 1510, 1490, 1455, 1440, 1250, 1120, 950, 750

20 Example 126

1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-4-(1-pyrrolidinylmethyl)piperazine



35 The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-(1-pyrrolidinylmethyl)piperazine instead of decylamine.

m.p. 212-214°C

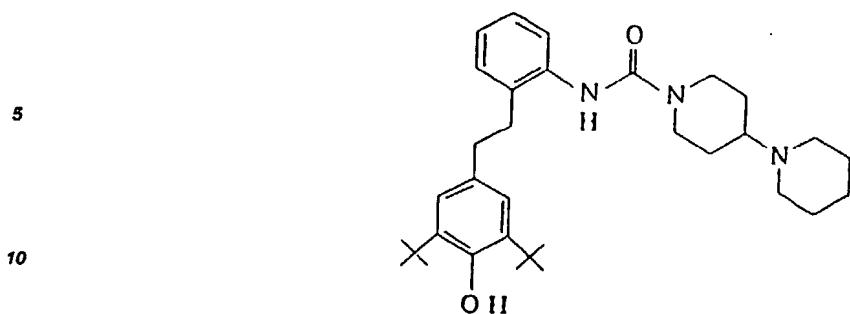
40 1H-NMR(δ ppm, CDCl₃) 7.47(d, J=8Hz, 1H), 7.16-7.25(m, 2H), 7.11(dd, J=7, 7, 1Hz, 1H), 6.78(s, 2H), 5.59(s, 1H), 5.10(s, 1H), 3.45-3.52(m, 4H), 3.28(t, J=5Hz, 4H), 3.11(s, 2H), 2.81(s, 4H), 2.50(t, J=5Hz, 4H), 1.80-2.00(m, 4H), 1.36(s, 18H)
IR(cm⁻¹) 3500, 3328, 2960, 1626, 1521, 1457, 1437, 750

45 Example 127

1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-4-piperidinopiperidine

50

55



The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-piperidinopiperidine instead of decylamine. m.p. 64-67°C

1H-NMR(δ ppm, CDCl₃) 7.48(d, J=7Hz, 1H), 7.16-7.25(m, 2H), 7.11(dd, J=7, 7, 2Hz, 1H), 6.79(s, 2H), 5.62(s, 1H), 5.09(s, 1H), 3.73-3.81(m, 2H), 2.81(s, 4H), 2.65-2.75(m, 2H), 2.44-2.51(m, 4H), 2.33-2.44(m, 1H), 1.75-1.82(m, 2H), 1.54-1.62(m, 4H), 1.39-1.50(m, 4H), 1.37(s, 18H)

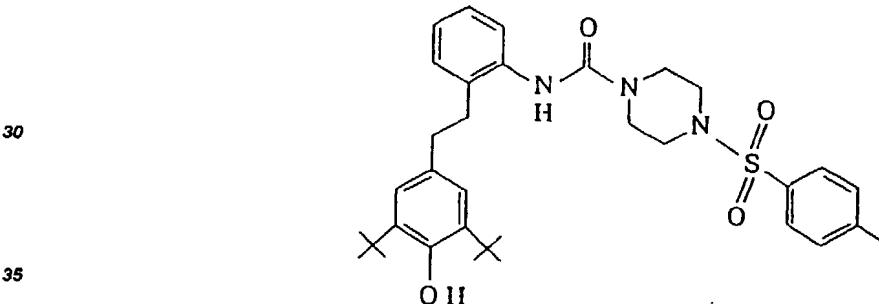
IR(cm⁻¹) 3636, 3420, 2934, 1640, 1520, 1450, 1250, 750

20

Example 128

1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-4-(p-toluenesulfonyl)piperazine

25



The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-(p-toluenesulfonyl)piperazine instead of decylamine.

40 m.p. 195-197°C

1H-NMR(δ ppm, CDCl₃) 7.61(d, J=8Hz, 2H), 7.29-7.36(m, 3H), 7.19-7.24(m, 3H), 6.73(s, 2H), 5.41(bs, 1H), 5.12(s, 1H), 3.26(t, J=5Hz, 4H), 2.93(t, J=5Hz, 4H), 2.70-2.83(m, 4H), 2.45(s, 3H), 1.35(s, 18H)

IR(cm⁻¹) 3630, 3410, 2950, 1635, 1625, 1350, 1170, 730

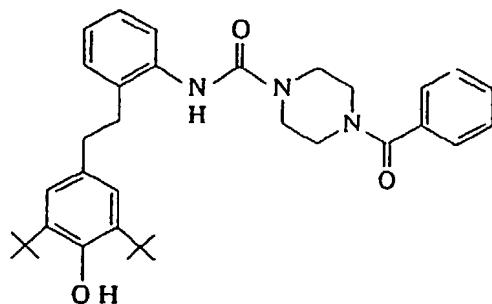
45 Example 129

1-Benzoyl-4-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]piperazine

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-benzoylpiperazine instead of decylamine. m.p. 207-209°C

15

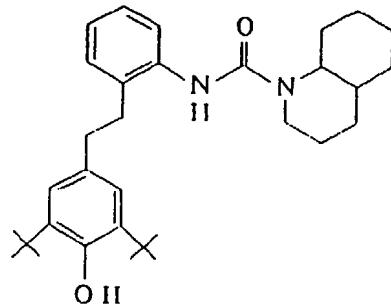
$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.37-7.48(m, 6H), 7.12-7.27(m, 3H), 6.76(s, 2H), 5.52(bs, 1H), 5.08(s, 1H), 3.12-3.85(m, 8H), 2.82(s, 4H), 1.33(s, 18H)
 $\text{IR}(\text{cm}^{-1})$ 3570, 3266, 2950, 1629, 1530, 1435, 1260, 1007, 754

Example 130

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1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]decahydroquinoline

25



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35

The title compound was prepared in a similar manner to that mentioned in Example 11, using decahydroquinoline instead of decylamine.

40

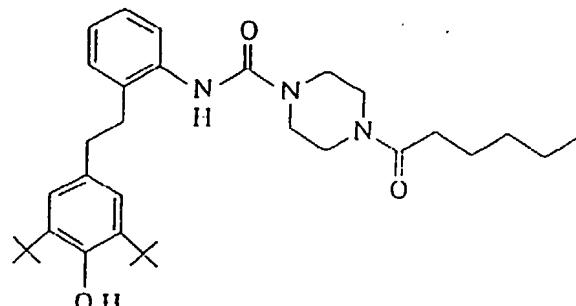
$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.57(d, $J=8\text{Hz}$, 1H), 7.12-7.21(m, 2H), 7.07(dd, $J=7, 7\text{Hz}$, 1H), 6.86(s, 2H), 5.88(bs, 1H), 5.08(s, 1H), 4.06(m, 1H), 3.45(m, 1H), 2.75-2.90(m, 5H), 1.90(m, 1H), 1.63-1.80(m, 4H), 1.20-1.60(m, 8H), 1.39(m, 18H)
 $\text{IR}(\text{cm}^{-1})$ 3430, 2924, 1632, 1510, 1434, 750

Example 131

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1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-4-pentanoylpiperazine

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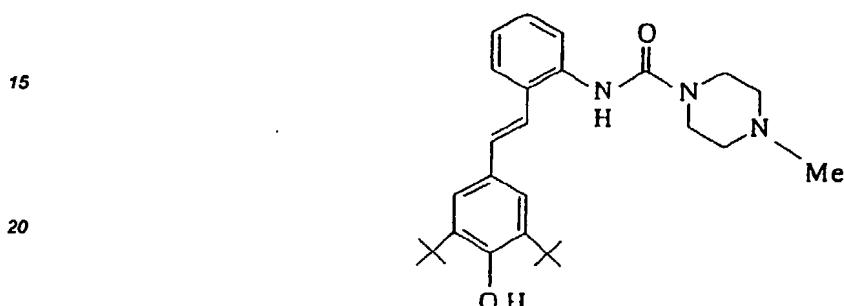
The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-pentanoylpiperazine instead of decylamine. m.p. 126-128°C

¹H-NMR(δ ppm, CDCl₃) 7.44(d, J=9Hz, 1H), 7.12-7.27(m, 3H), 6.77(s, 2H), 5.52(bs, 1H), 5.12(s, 1H), 3.56-3.63(m, 2H), 3.40-3.46(m, 2H), 3.27-3.34(m, 2H), 3.08-3.14(m, 2H), 2.82(s, 4H), 2.30(t, J=5Hz, 2H), 1.58-1.67(m, 2H), 1.36(s, 18H), 1.28-1.38(m, 4H)

IR(cm⁻¹) 3300, 2952, 1636, 1530, 1435, 1240, 994, 755

Example 132

10 1-[N-[2-(3,5-di-tert-butyl-4-hydroxystyryl)phenyl]carbamoyl]-4-methylpiperazine



25 The title compound was prepared in a similar manner to that mentioned in Example 101, using 1-methylpiperazine instead of 2-(aminomethyl)pyridine. m.p. 192-194°C

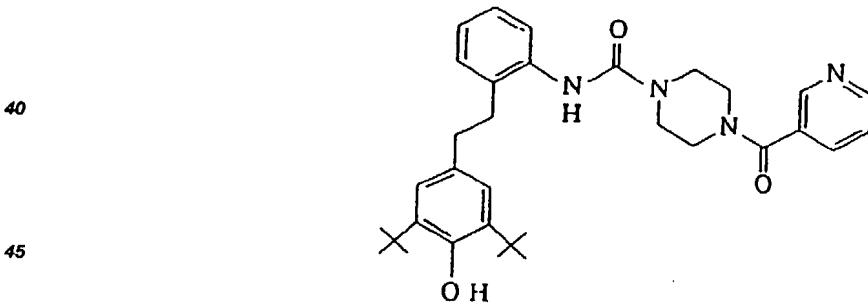
¹H-NMR(δ ppm, CDCl₃) 7.65(d, J=8Hz, 1H), 7.46-7.50(m, 1H), 7.33(s, 2H), 7.20-7.26(m, 1H), 7.11(dd, J=9, 1Hz, 1H), 6.99(d, J=16Hz, 1H), 6.94(d, J=16Hz, 1H), 6.39(bs, 1H), 5.34(s, 1H), 3.51(t, J=5Hz, 4H), 2.43(t, J=5Hz, 4H), 2.32(m, 3H), 1.47(s, 18H)

30 IR(cm⁻¹) 3636, 3420, 3288, 2952, 1635, 1525, 1485, 1439, 1236, 1149, 959, 765, 755

Example 133

1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-4-nicotinoylpiperazine

35



50 The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-nicotinoylpiperazine instead of decylamine. m.p. 171-172°C

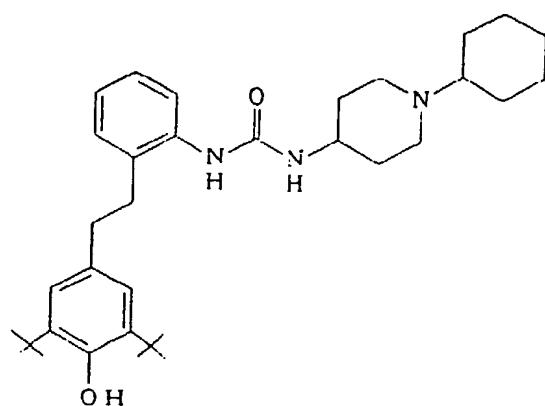
¹H-NMR(δ ppm, CDCl₃) 8.70(dd, J=5, 2Hz, 1H), 8.66(d, J=1Hz, 1H), 7.75(ddd, J=8, 8, 2Hz, 1H), 7.36-7.42(m, 2H), 7.14-7.27(m, 3H), 6.75(s, 2H), 5.52(s, 1H), 5.11(s, 1H), 3.10-3.80(m, 8H), 2.82(s, 4H), 1.33(s, 18)

IR(cm⁻¹) 3636, 3420, 3288, 2952, 1635, 1525, 1485, 1439, 1236, 1149, 959, 765, 755

55 **Example 134**

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-cyclohexyl-4-piperidyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-amino-1-cyclohexylpiperidine instead of decylamine.

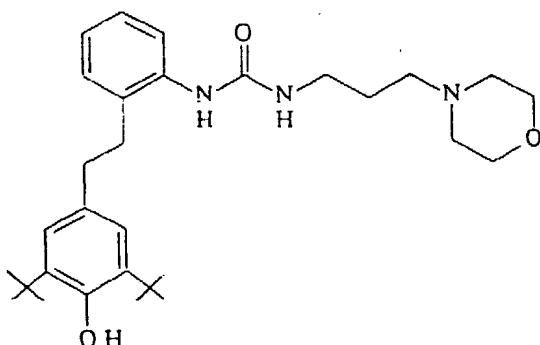
20 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.15-7.25(m, 4H), 6.79(s, 2H), 5.38(bs, 2H), 5.12(s, 1H), 4.55(bs, 1H), 3.65-3.75(m, 1H), 2.90-2.98(m, 2H), 2.75-2.90(m, 4H), 2.35-2.45(m, 3H), 1.85-2.00(m, 4H), 1.78(bs, 2H), 1.45-1.65(m, 3H), 1.38(s, 18H), 1.00-1.35(m, 5H)
 25 $\text{IR(cm}^{-1}\text{)}$ 3638, 3262, 1658, 1643, 1560, 1542, 1435, 1233, 754

Example 135

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N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(3-morpholinopropyl)urea

30



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40

The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-(3-aminopropyl)morpholine instead of decylamine. m.p. 138-139°C

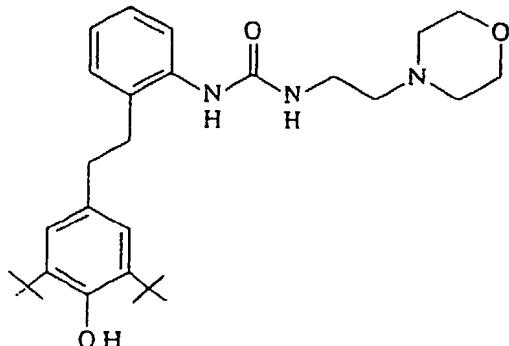
45 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.19-7.29(m, 4H), 6.80(s, 2H), 5.19(bs, 1H), 5.12(s, 1H), 5.04(t, $J=5\text{Hz}$, 1H), 3.44(bs, 4H), 3.25(q, $J=6\text{Hz}$, 2H), 2.77-2.87(m, 4H), 2.25-2.35(m, 6H), 1.60(quint., $J=7\text{Hz}$, 2H), 1.38(s, 18H)
 50 $\text{IR(cm}^{-1}\text{)}$ 3528, 3304, 1633, 1565, 1436, 1238, 1116, 872, 752

Example 136

55 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(2-morpholinoethyl)urea

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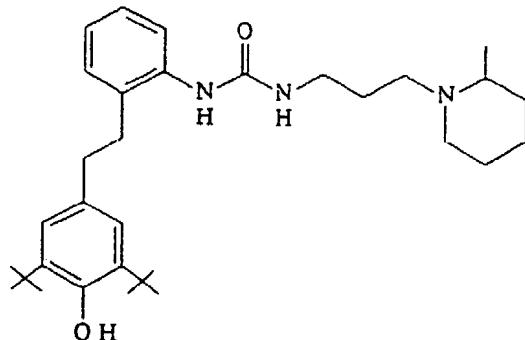
Example 137

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(3-(2-methyl-1-piperidyl)propyl)urea

25

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-(3-aminopropyl)-2-methylpiperidine instead of decylamine.

¹H-NMR(δ ppm, CDCl₃) 7.14-7.30(m, 4H), 6.81(s, 2H), 5.43(bs, 1H), 5.36(bs, 1H), 5.11(s, 1H), 3.15-3.30(m, 2H), 2.70-2.87(m, 6H), 2.20-2.30(m, 2H), 2.01(t, J=10Hz, 1H), 1.40-1.65(m, 5H), 1.38(s, 18H), 1.00-1.40(m, 3H), 0.98(d, J=6Hz, 3H)

IR(cm⁻¹) 3638, 3294, 1643, 1543, 1436, 1234, 754

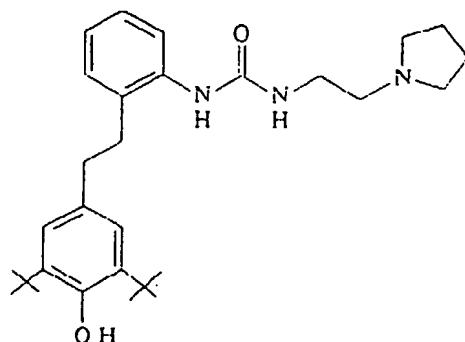
Example 138

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(2-(1-pyrrolidinyl)ethyl)urea

50

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15 The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-(2-aminooethyl)pyrrolidine instead of decylamine.

¹H-NMR(δ ppm, CDCl₃) 7.37(d, J=7Hz, 1H), 7.11-7.21(m, 3H), 6.82(s, 2H), 5.55(bs, 1H), 5.26(s, 1H), 5.03(s, 1H), 3.29(t, J=6Hz, 2H), 2.65-2.85(m, 5H), 2.59(t, J=6Hz, 2H), 2.53(bs, 3H), 1.74(bs, 4H), 1.38(s, 18H)
IR(cm⁻¹) 3638, 3350, 1686, 1546, 1436, 1234, 753

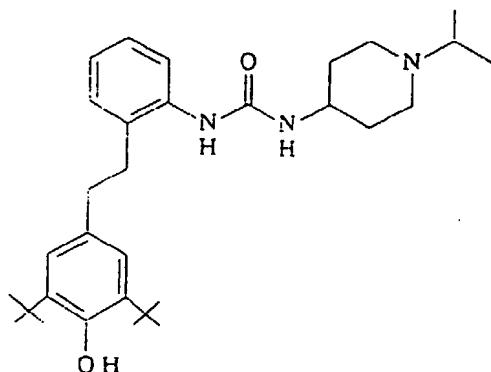
20

Example 139

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[1-(2-propyl)-4-piperidyl]urea

25

30



35

40

The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-amino-1-(2-propyl)piperidine instead of decylamine. m.p. 191-193°C

¹H-NMR(δ ppm, CDCl₃) 7.15-7.26(m, 4H), 6.78(s, 2H), 5.11(bs, 2H), 4.30(bs, 1H), 3.59-3.72(m, 1H), 2.73-2.90(m, 7H), 2.25-2.37(m, 2H), 1.87-1.98(m, 2H), 1.30-1.50(m, 2H), 1.38(s, 18H), 1.07(d, J=6Hz, 6H)
IR(cm⁻¹) 3358, 2948, 1641, 1561, 1435, 1235

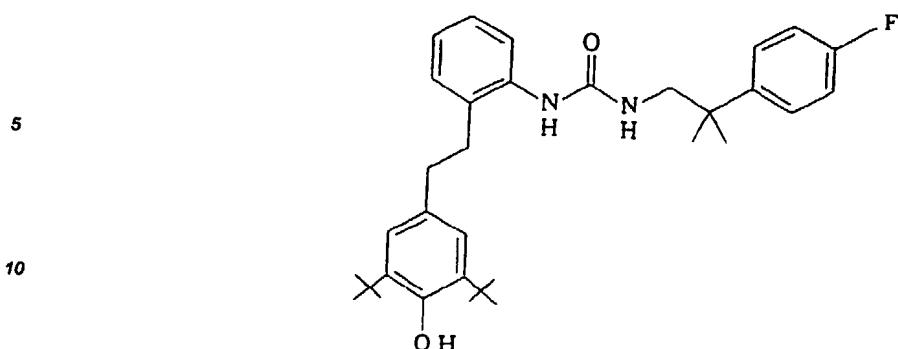
45

Example 140

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[2-(4-fluorophenyl)-2-methylpropyl]urea

50

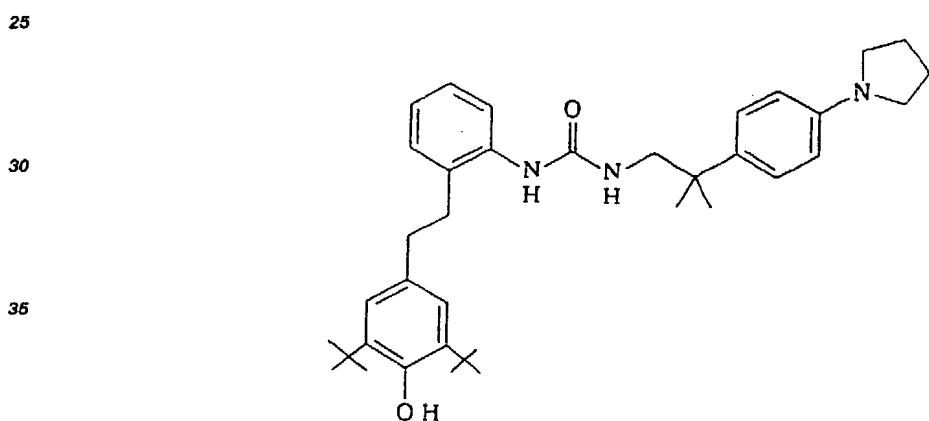
55



15 The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-fluoro- β,β -dimethylphenethylamine instead of decylamine. m.p. 179-180°C
 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.14-7.20(m, 4H), 7.08(t, $J=7\text{Hz}$, 1H), 6.87-6.96(m, 3H), 6.74(s, 2H), 5.08(s, 1H), 5.00(s, 1H), 3.95-4.05(m, 1H), 3.30(d, $J=6\text{Hz}$, 2H), 2.70-2.80(m, 4H), 1.36(s, 18H), 1.24(s, 6H)
 $\text{IR(cm}^{-1}\text{)}$ 3638, 3370, 1644, 1653, 1613, 1436, 1231, 1166, 833, 762

20 Example 141

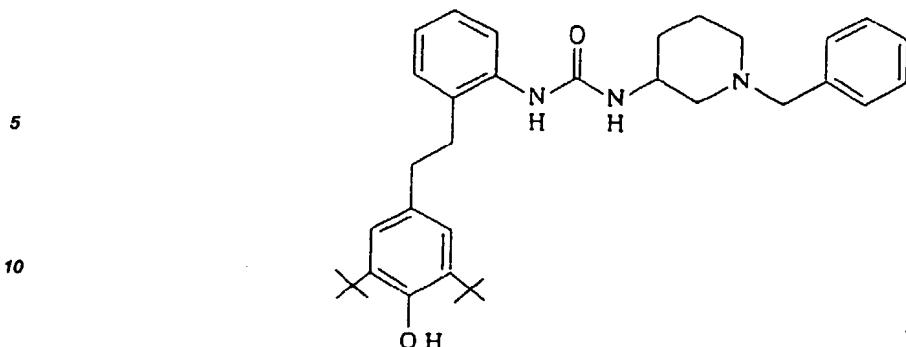
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[2-[4-(1-pyrrolidinyl)phenyl]-2-methylpropyl]urea



40 The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-[4-(1-amino-2-methyl-2-propyl)phenyl]pyrrolidine instead of decylamine.
m.p. 195-196°C
 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.02-7.18(m, 6H), 6.77(s, 2H), 6.43(d, $J=9\text{Hz}$, 2H), 5.08(s, 2H), 4.14(t, $J=6\text{Hz}$, 1H), 3.28(t, $J=6\text{Hz}$, 2H), 3.22-3.25(m, 4H), 2.70-2.78(m, 4H), 1.97-2.01(m, 4H), 1.37(s, 18H), 1.23(s, 6H)
 $\text{IR(cm}^{-1}\text{)}$ 3642, 3354, 1642, 1615, 1562, 1524, 1369, 1234, 814, 750

Example 142

50 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-benzyl-3-piperidyl)urea



15 The title compound was prepared in a similar manner to that mentioned in Example 11, using 3-amino-1-benzylpiperidine instead of decylamine.

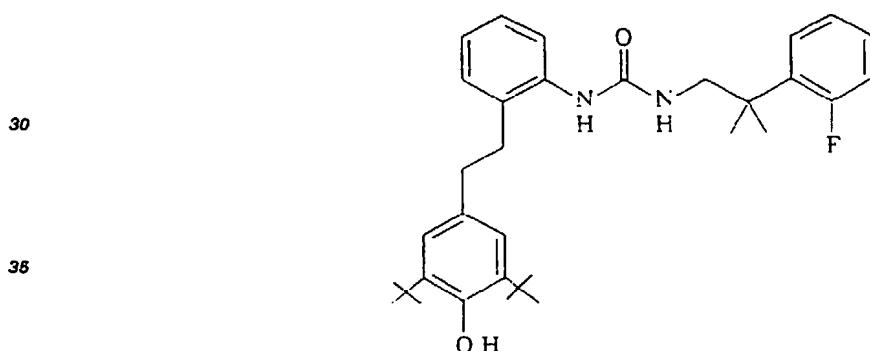
1H-NMR(δ ppm, CDCl_3) 7.20-7.40(m, 9H), 6.79(s, 2H), 5.12(bs, 1H), 5.09(s, 1H), 3.87-3.96(m, 1H), 3.49(bs, 1H), 3.37(d, $J=13\text{Hz}$, 1H), 3.28(d, $J=13\text{Hz}$, 1H), 2.70-2.90(m, 4H), 2.40-2.50(m, 2H), 1.30-1.70(m, 24H)

20 IR(cm^{-1}) 3632, 3338, 2948, 1639, 1542, 1435, 1234, 744, 699

Example 143

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[2-(2-fluorophenyl)-2-methylpropyl]urea

25



40 The title compound was prepared in a similar manner to that mentioned in Example 11, using 2-fluoro- β,β -dimethylphenethylamine instead of decylamine. m.p. 182-183°C

1H-NMR(δ ppm, CDCl_3) 6.88-7.21(m, 8H), 6.75(s, 2H), 5.07(s, 1H), 5.02(s, 1H), 4.02-4.09(m, 1H), 3.50(d, $J=6\text{Hz}$, 2H), 2.67-2.78(m, 4H), 1.36(s, 18H), 1.33(s, 6H)

IR(cm^{-1}) 3650, 3330, 2960, 1640, 1575, 1445, 1255, 765

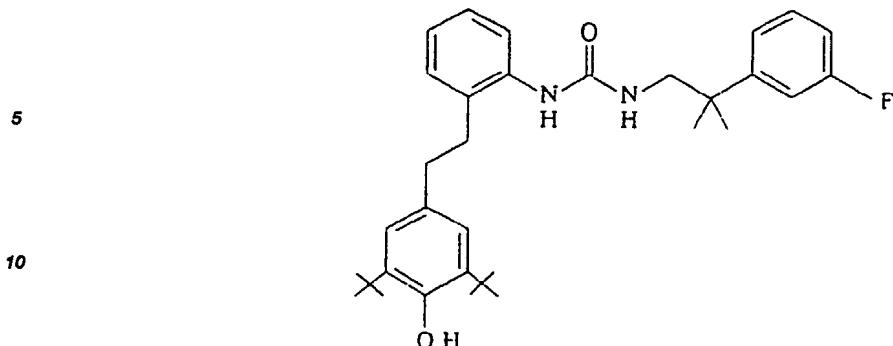
45

Example 144

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[2-(3-fluorophenyl)-2-methylpropyl]urea

50

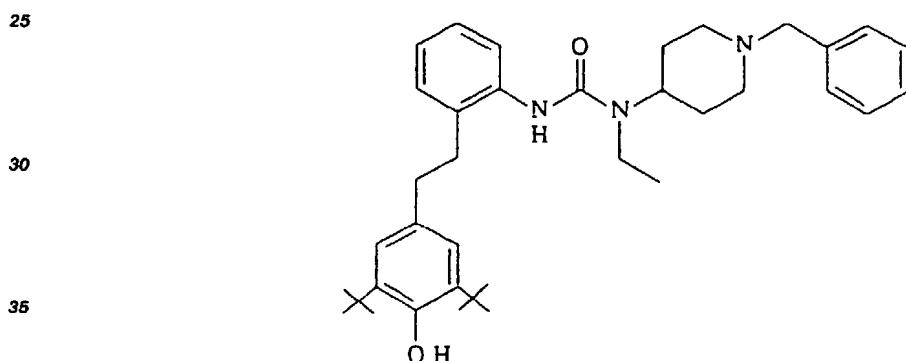
55



The title compound was prepared in a similar manner to that mentioned in Example 11, using 3-fluoro- β,β -dimethylphenethylamine instead of decylamine. m.p. 165-166°C
 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.04-7.23(m, 4H), 6.80-7.00(m, 4H), 6.74(s, 2H), 5.08(s, 1H), 4.94(s, 1H), 3.98(t, $J=6\text{Hz}$, 1H), 3.32(d, $J=6\text{Hz}$, 2H), 2.68-2.79(m, 4H), 1.36(s, 18H), 1.25(s, 6H)
 $\text{IR}(\text{cm}^{-1})$ 3640, 3350, 2970, 1645, 1615, 1590, 1560, 1440, 910, 765, 700

20
Example 145

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-benzyl-4-piperidyl)-N'-ethylurea



The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-ethylamino-
40 1-benzylpiperidine instead of decylamine. m.p. 149-151°C
 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.72(d, $J=8\text{Hz}$, 1H), 7.15-7.33(m, 7H), 7.07(t, $J=7\text{Hz}$, 1H), 6.83(s, 2H), 5.91(bs, 1H), 5.07(s, 1H), 4.16-4.38(m, 1H), 3.48(s, 2H), 3.02(q, $J=7\text{Hz}$, 2H), 2.93(d, $J=12\text{Hz}$, 2H), 2.82(bs, 4H), 2.03-2.10(m, 2H), 1.60-1.75(m, 4H), 1.37(s, 18H), 1.16(t, $J=7\text{Hz}$, 3H)
 $\text{IR}(\text{cm}^{-1})$ 3334, 2954, 1631, 1520, 1502, 1263, 1202, 743

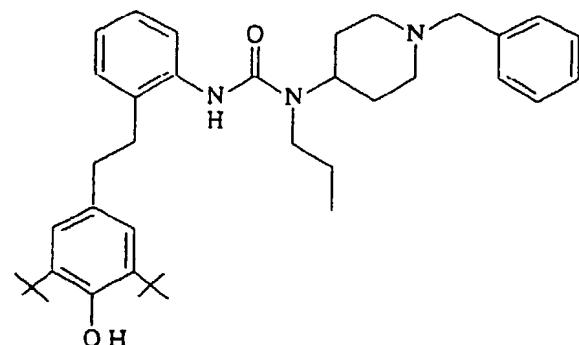
45
Example 146

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-benzyl-4-piperidyl)-N'-propylurea

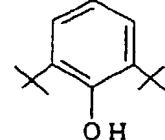
50

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15 The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-benzyl-4-propylaminopiperidine instead of decylamine.

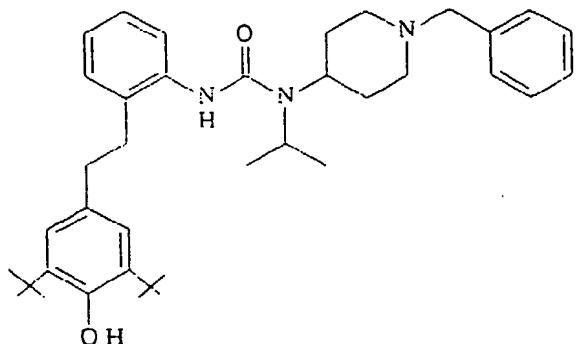
¹H-NMR(δ ppm, CDCl₃) 7.76(d, J=7Hz, 1H), 7.10-7.35(m, 7H), 7.04(td, J=6, 1Hz, 1H), 6.87(s, 2H), 6.07(bs, 1H), 5.06(s, 1H), 4.12-4.23(m, 1H), 3.48(s, 2H), 3.04(bt, J=8Hz, 2H), 2.94(d, J=12Hz, 2H), 2.81(s, 4H), 2.00-2.10(m, 2H), 1.50-1.75(m, 6H), 1.39(s, 18H), 0.86(t, J=7Hz, 3H)

20 IR(cm⁻¹) 3634, 3450, 2956, 1650, 1509, 1451, 1234, 742

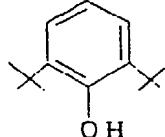
Example 147

25 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-benzyl-4-piperidyl)-N'-(2-propyl)urea

30



35



40 The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-benzyl-4-[(2-propyl)amino]piperidine instead of decylamine.

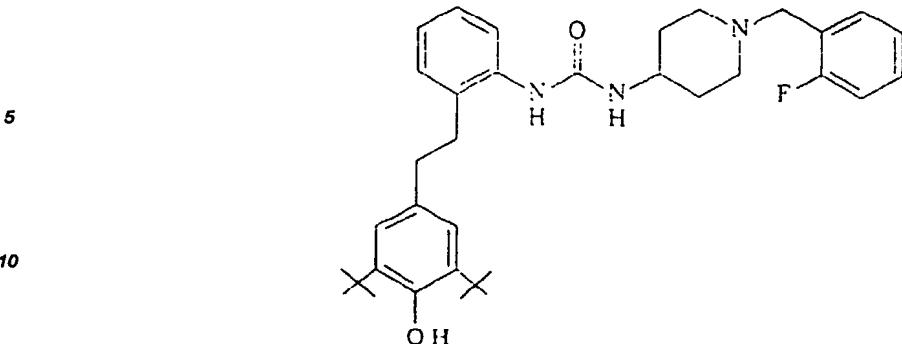
¹H-NMR(δ ppm, CDCl₃) 7.65(d, J=8Hz, 1H), 7.10-7.30(m, 7H), 7.04(td, J=7, 1Hz, 1H), 6.89(s, 2H), 6.03(bs, 1H), 5.05(s, 1H), 3.70-3.90(m, 2H), 3.47(s, 2H), 2.75-2.98(m, 6H), 1.90-2.05(m, 4H), 1.55-1.70(m, 2H), 1.39(s, 18H), 1.31(d, J=7Hz, 6H)

45 IR(cm⁻¹) 3450, 2954, 1650, 1521, 1451, 1237, 744

Example 148

50 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[1-(2-fluorobenzyl)-4-piperidyl]urea

55



15 The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-amino-1-(2-fluorobenzyl)piperidine instead of decylamine.

m.p. 136-137°C

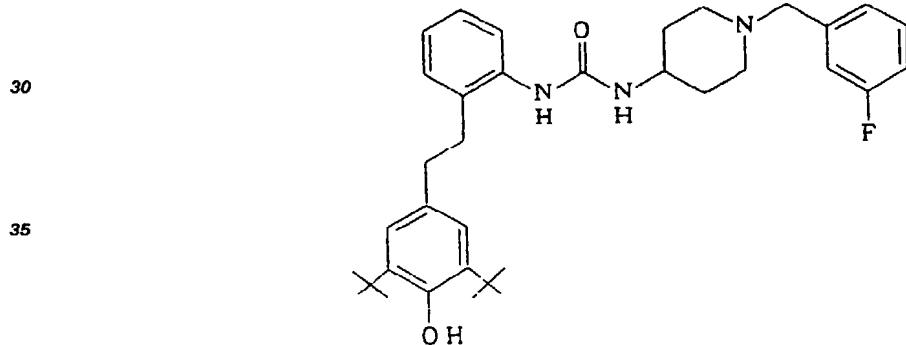
1H-NMR(δ ppm, CDCl_3) 7.14-7.34(m, 6H), 6.95-7.10(m, 2H), 6.77(s, 2H), 5.10(s, 1H), 4.99(s, 1H), 4.10(d, $J=8\text{Hz}$, 1H), 3.55-3.71(m, 1H), 3.52(s, 2H), 2.68-2.88(m, 6H), 2.07-2.17(m, 2H), 1.82-1.90(m, 2H),

20 1.37(s, 18H), 1.24-1.35(m, 2H)

IR(cm^{-1}) 3640, 3340, 2960, 1650, 1590, 1570, 1495, 1235, 765

Example 149

25 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-(3-fluorobenzyl)-4-piperidyl)urea



40

The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-amino-1-(3-fluorobenzyl)piperidine instead of decylamine. m.p. 99-100°C

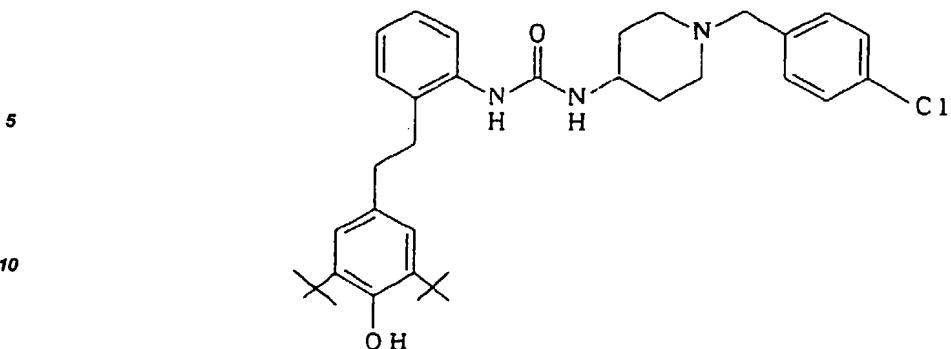
1H-NMR(δ ppm, CDCl_3) 7.15-7.27(m, 5H), 7.67-7.04(m, 2H), 6.86-6.94(m, 1H), 5.10(s, 1H), 4.12(d, $J=8\text{Hz}$, 1H), 3.57-3.70(m, 1H), 3.42(s, 2H), 2.66-2.86(m, 6H), 2.06(t, $J=12\text{Hz}$, 2H), 1.86(d, $J=12\text{Hz}$, 2H), 1.38(s, 18H), 1.24-1.35(m, 2H)

IR(cm^{-1}) 3635, 3340, 2950, 1640, 1590, 1565, 1490, 1440, 1235, 880, 750, 690

Example 150

50 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-(4-chlorobenzyl)-4-piperidyl)urea

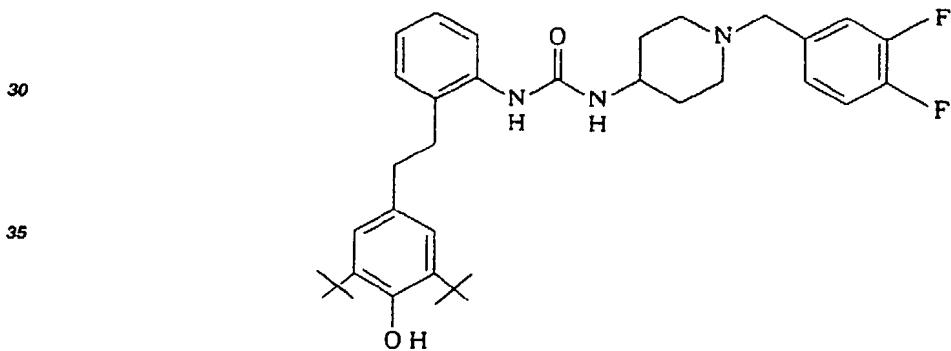
55



1H-NMR(δ ppm, CDCl_3) 7.15-7.32(m, 8H), 6.77(s, 2H), 5.10(s, 1H), 4.98(s, 1H), 4.09(d, $J=8\text{Hz}$, 1H), 3.57-3.70(m, 1H), 3.39(s, 2H), 2.74-2.87(m, 4H), 2.69(d, $J=11\text{Hz}$, 2H), 2.04(t, $J=11\text{Hz}$, 2H), 1.81-1.88(m, 2H), 1.37(s, 18H), 1.14-1.22(m, 2H)
IR(cm^{-1}) 3645, 3360, 2940, 1640, 1590, 1555, 1490, 1435, 1295, 1235, 1095, 750

Example 151

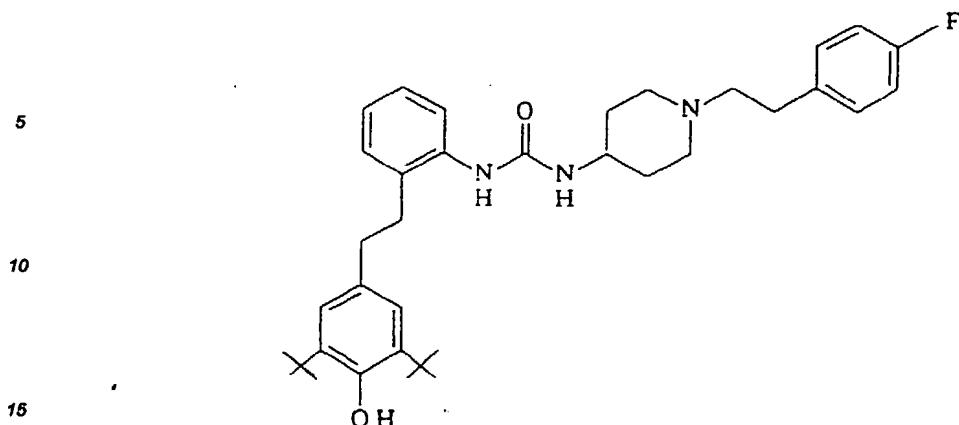
25 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-(3,4-difluorobenzyl)-4-piperidyl)urea



1H-NMR(δ ppm, CDCl_3) 6.92-7.28(m, 7H), 6.77(s, 2H), 5.10(s, 1H), 4.97(s, 1H), 4.08(d, $J=8\text{Hz}$, 1H), 3.58-3.72(m, 1H), 3.37(s, 2H), 2.74-2.87(m, 4H), 2.05(t, $J=11\text{Hz}$, 2H), 1.82-1.90(m, 2H), 1.38(s, 18H), 1.24-1.35(m, 2H)
IR(cm^{-1}) 3650, 3370, 2965, 1645, 1570, 1525, 1440, 1295, 1240, 885, 785, 765

Example 152

50 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-(4-fluorophenethyl)-4-piperidyl)urea



The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-amino-1-(4-fluorophenethyl)piperidine instead of decylamine.

20 m.p. 117-119°C

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.10-7.20(m, 6H), 6.94(td, $J=7, 2\text{Hz}$, 2H), 6.78(s, 2H), 5.11(s, 1H), 5.04(bs, 1H), 4.13(bd, $J=8\text{Hz}$, 1H), 3.58-3.70(m, 1H), 2.70-2.90(m, 8H), 2.45-2.55(m, 2H), 2.08-2.12(m, 2H), 1.85-1.95(m, 2H), 1.30-1.40(m, 2H), 1.38(s, 18H)

25 $\text{IR(cm}^{-1}\text{)}$ 3630, 3314, 2948, 1634, 1565, 1510, 1228, 748

25

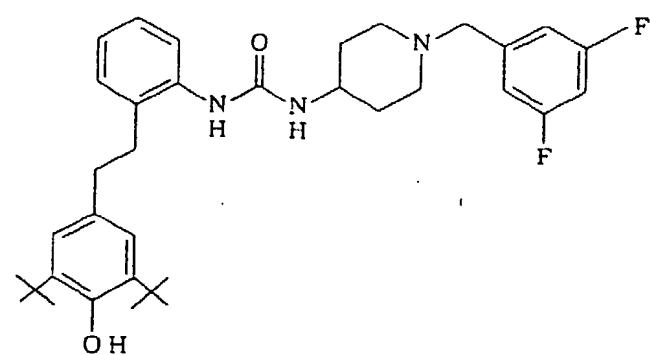
Example 153

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-(3,5-difluorobenzyl)-4-piperidyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-amino-1-(3,5-difluorobenzyl)piperidine instead of decylamine.

45 m.p. 119-120°C

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.17-7.28(m, 4H), 6.82(d, $J=6\text{Hz}$, 2H), 6.77(s, 2H), 6.62-6.69(m, 1H), 5.11(s, 1H), 4.97(s, 1H), 4.09(d, $J=8\text{Hz}$, 1H), 3.58-3.71(m, 1H), 3.40(s, 2H), 2.66-2.88(m, 6H), 2.07(t, $J=11\text{Hz}$, 2H), 1.83-1.92(m, 2H), 1.38(s, 18H), 1.25-1.36(m, 2H)

50

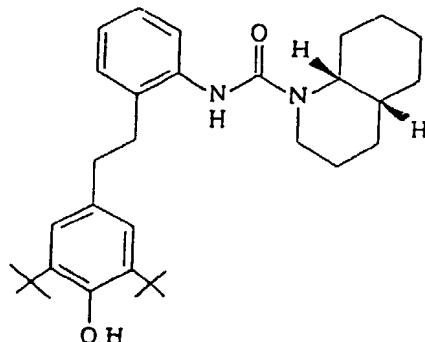
$\text{IR(cm}^{-1}\text{)}$ 3640, 3350, 2960, 1635, 1605, 1505, 1440, 1325, 1235, 1120, 995, 855

Example 154

2-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-cis-decahydroquinoline

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15 The title compound was prepared in a similar manner to that mentioned in Example 11, using *cis*-decahydroquinoline instead of decylamine. m.p. 132-133°C

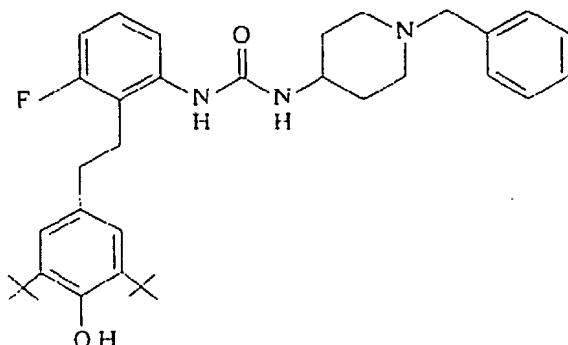
1H-NMR(δ ppm, CDCl₃) 7.64(d, J=8Hz, 1H), 7.23-7.30(m, 2H), 7.11(t, J=7Hz, 1H), 6.93(s, 2H), 5.94(s, 1H), 5.14(s, 1H), 4.09-4.20(m, 1H), 3.48-3.59(m, 1H), 2.83-2.94(m, 5H), 1.50-2.00(m, 9H), 1.45(s, 18H), 1.24-1.42(m, 4H)

20 IR(cm⁻¹) 3640, 3320, 2925, 2860, 1630, 1515, 1435, 1360, 1275, 1235, 1160, 755

Example 155

25 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-3-fluorophenyl]-N'-(1-benzyl-4-piperidyl)urea

30



35

40 The title compound was prepared in a similar manner to that mentioned in Example 108, using 4-(2-amino-6-fluorophenethyl)-2,6-di-tert-butylphenol instead of 4-(2-amino-3,5-difluorophenethyl)-2,6-di-tert-butylphenol.

m.p. 103-105°C

45 1H-NMR(δ ppm, CDCl₃) 7.20-7.35(m, 5H), 7.13(t, J=8Hz, 1H), 7.03(d, J=8Hz, 1H), 6.93(t, J=9Hz, 1H), 6.75(s, 2H), 5.13(s, 1H), 4.60(bs, 1H), 3.95(bd, J=8Hz, 1H), 3.54-3.66(m, 1H), 3.44(s, 2H), 2.70-2.90(m, 6H), 2.00-2.10(m, 2H), 1.80-1.90(m, 2H), 1.30-1.40(m, 2H), 1.36(s, 18H)

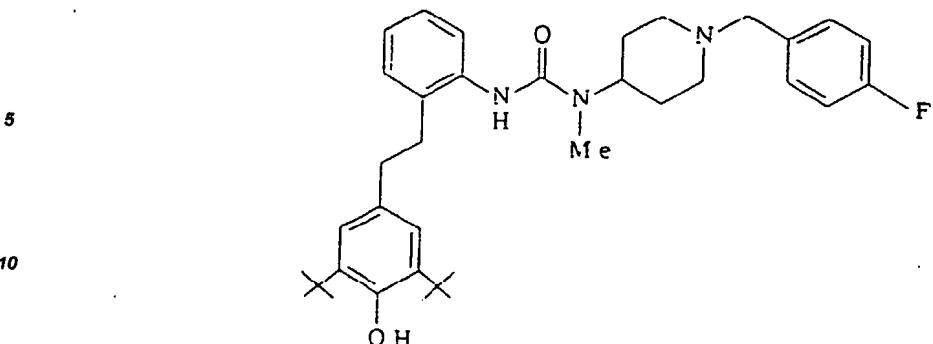
IR(cm⁻¹) 3630, 3300, 2948, 1632, 1565, 1452, 1235, 699

Example 156

50

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-(4-fluorobenzyl)-4-piperidyl)-N'-methylurea

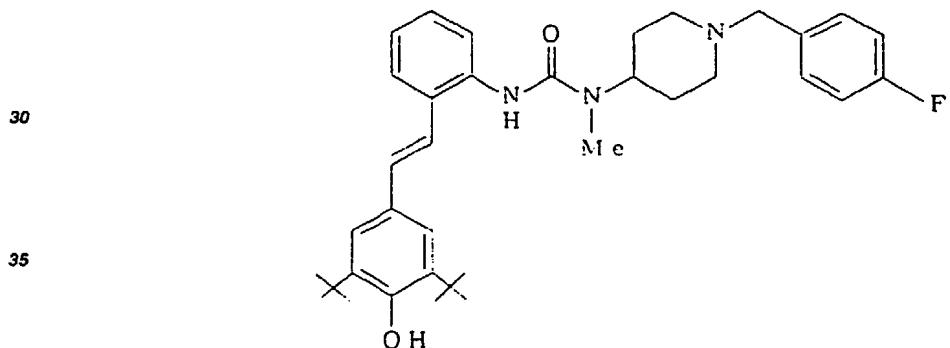
55



15 The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-(4-fluorobenzyl)-4-(methylamino)piperidine instead of decylamine. m.p. 177-178°C
¹H-NMR(δ ppm, CDCl₃) 7.63(d, J=8Hz, 1H), 7.17-7.28(m, 4H), 7.08-7.13(m, 1H), 6.95-7.03(m, 2H), 6.78(s, 2H), 5.61(s, 1H), 5.08(s, 1H), 4.17-4.28(m, 1H), 3.43(s, 2H), 2.90(d, J=12Hz, 2H), 2.81(s, 4H), 2.50(s, 3H), 1.98-2.07(m, 2H), 1.54-1.68(m, 4H), 1.35(s, 18H)
20 IR(cm⁻¹) 3630, 3330, 2970, 1635, 1520, 1440, 1330, 1230, 1050, 760,

Example 157

25 N-[2-(3,5-di-tert-butyl-4-hydroxystyryl)phenyl]-N'-[1-(4-fluorobenzyl)-4-piperidyl]-N'-methylurea



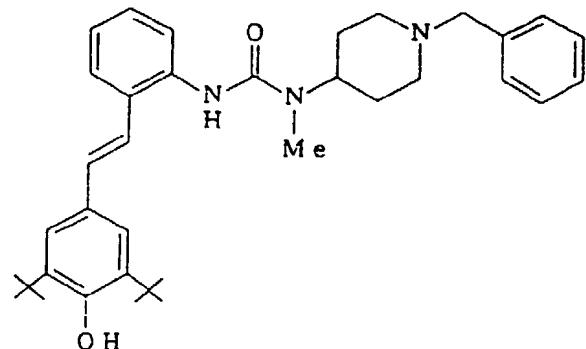
40 The title compound was prepared in a similar manner to that mentioned in Example 101, using 1-(4-fluorobenzyl)-4-(methylamino)piperidine instead of 2-(aminomethyl)pyridine. m.p. 174-175°C
¹H-NMR(δ ppm, CDCl₃) 7.79(d, J=8Hz, 1H), 7.45(dd, J=7, 1Hz, 1H), 7.31(s, 2H), 7.20-7.30(m, 3H), 7.05-7.13(m, 1H), 6.93-7.03(m, 4H), 6.38(s, 1H), 5.32(s, 1H), 4.14-4.26(m, 1H), 3.46(s, 2H), 2.85-2.96(m, 5H), 1.99-2.10(m, 2H), 1.63-1.82(m, 4H), 1.46(s, 18H)
45 IR(cm⁻¹) 3640, 3450, 2960, 1640, 1510, 1225, 1160, 1045, 965, 760

Example 158

50 N-[2-(3,5-di-tert-butyl-4-hydroxystyryl)phenyl]-N'-(1-benzyl-4-piperidyl)-N'-methylurea

55

5



10

15 The title compound was prepared in a similar manner to that mentioned in Example 101, using 1-benzyl-4-(methylamino)piperidine instead of 2-(aminomethyl)pyridine. m.p. 163-164°C

¹H-NMR(δ ppm, CDCl₃) 7.78(d, J=7Hz, 1H), 7.45(dd, J=8, 1Hz, 1H), 7.20-7.35(m, 8H), 7.04-7.12(m, 1H), 7.00(d, J=16Hz, 1H), 6.93(d, J=16Hz, 1H), 6.38(s, 1H), 5.32(s, 1H), 4.14-4.27(m, 1H), 3.48(s, 2H), 2.94(d, J=12Hz, 2H), 2.90(s, 3H), 2.00-2.11(m, 2H), 1.60-1.84(m, 4H), 1.46(s, 18H)

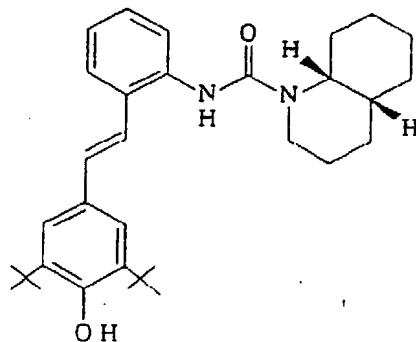
20 IR(cm⁻¹) 3625, 3440, 3260, 2960, 1635, 1530, 1485, 1240, 1150, 1045, 960, 755, 745, 700

Example 159

2-[N-[2-(3,5-di-tert-butyl-4-hydroxystyryl)phenyl]carbamoyl]-cis-dehydroquinoline

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The title compound was prepared in a similar manner to that mentioned in Example 101, using cis-dehydroquinoline instead of 2-(aminomethyl)pyridine.

¹H-NMR(δ ppm, CDCl₃) 7.71(d, J=8Hz, 1H), 7.46(d, J=6Hz, 1H), 7.33(s, 2H), 7.20-7.28(m, 1H), 7.05-7.11(m, 1H), 7.00(d, J=16Hz, 1H), 6.93(d, J=16Hz, 1H), 6.41(s, 1H), 5.32(s, 1H), 3.85-4.07(m, 2H), 1.68-1.97(m, 5H), 1.47-1.64(m, 5H), 1.47(s, 18H), 1.18-1.43(m, 3H)

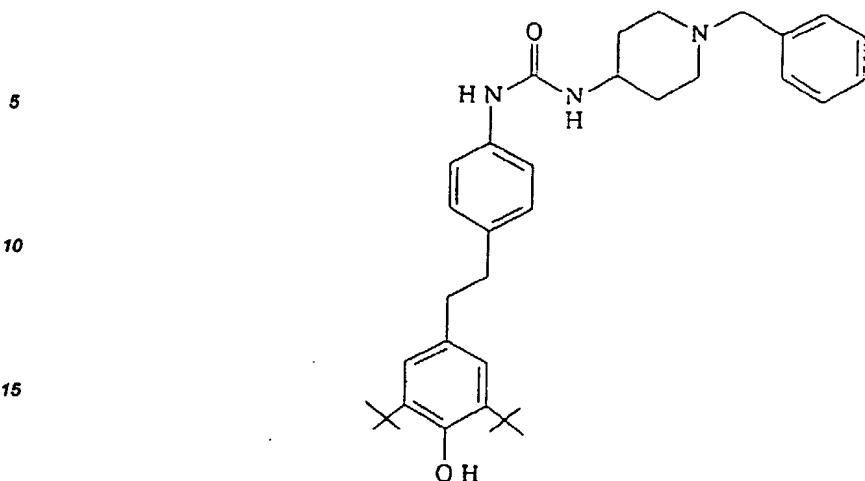
45 IR(cm⁻¹) 3640, 3450, 3300, 2930, 2870, 1645, 1525, 1445, 1240, 1160, 965, 755

Example 160

N-[4-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(1-benzyl-4-piperidyl)urea

50

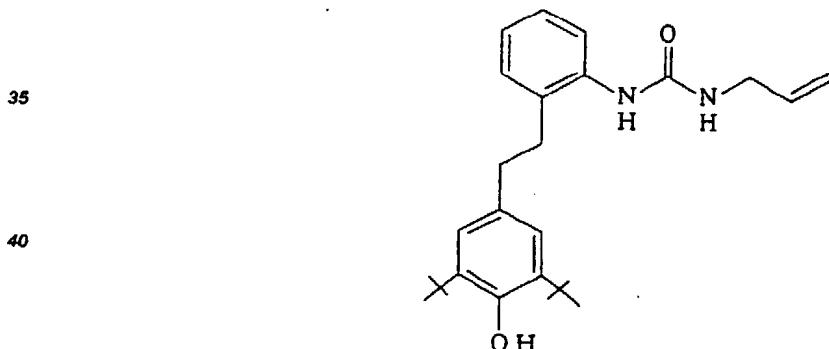
55



20 The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-(4-aminophenethyl)-2,6-di-tert-butylphenol instead of 4-(2-aminophenethyl)-2,6-di-tert-butylphenol and using 4-amino-1-benzylpiperidine instead of decylamine. m.p. 195-197°C
¹H-NMR(δ ppm, CDCl₃) 7.22-7.34(m, 5H), 7.15(s, 4H), 6.92(s, 2H), 6.10(s, 1H), 5.06(s, 1H), 4.56(d, J=8Hz, 1H), 3.66-3.78(m, 1H), 3.49(s, 2H), 2.75-2.90(m, 6H), 2.07-2.18(m, 2H), 1.91-1.99(m, 2H), 1.36-1.47(m, 2H), 1.43(s, 18H)
IR(cm⁻¹) 3620, 3378, 2946, 1659, 1604, 1542, 1515, 1435, 1324, 1234, 740

Example 161

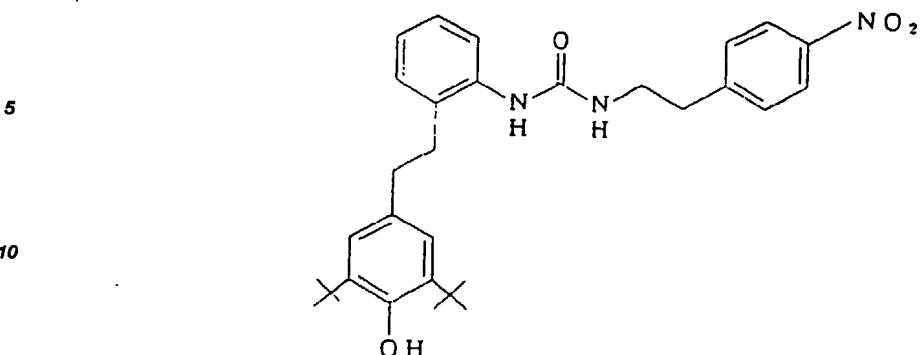
30 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-allylurea



45 The title compound was prepared in a similar manner to that mentioned in Example 11, using allylamine instead of decylamine. m.p. 169-172°C
¹H-NMR(δ ppm, CDCl₃) 7.16-7.32(m, 5H), 6.78(s, 2H), 5.73-5.85(m, 1H), 4.96-5.14(m, 3H), 4.20-4.26(m, 1H), 3.73-3.80(m, 2H), 2.76-2.90(m, 4H), 1.37(s, 18H)
IR(cm⁻¹) 3632, 3334, 2956, 1653, 1587, 1570, 1561, 1436, 1235, 924, 769

Example 162

55 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(4-nitrophenethyl)urea



The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-nitrophenethylamine instead of decylamine. m.p. 134-136°C

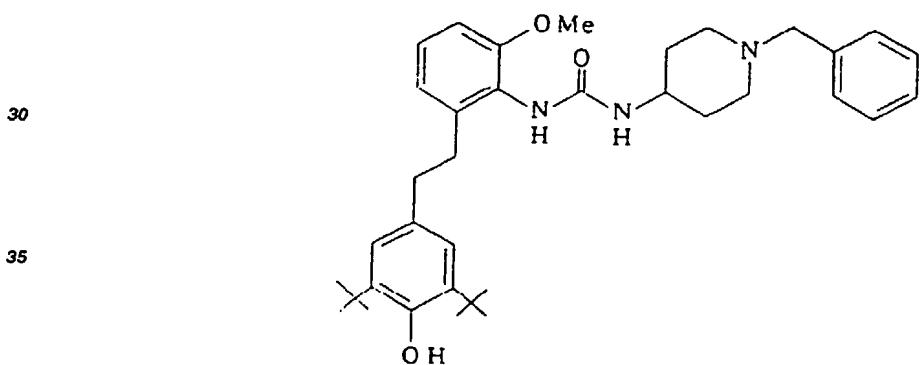
¹H-NMR(δ ppm, CDCl₃) 8.08(d, J=8Hz, 1H), 7.10-7.29(m, 6H), 6.75(s, 2H), 5.12(s, 1H), 5.05(s, 1H), 4.28(t, J=6Hz, 1H), 3.39(td, J=7, 6Hz, 2H), 2.73-2.90(m, 6H), 1.35(s, 18H)

20 IR(cm⁻¹) 3630, 3314, 2954, 1639, 1561, 1519, 1436, 1347, 753

Example 163

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-8-methoxyphenyl]-N'-(1-benzyl-4-piperidyl)urea

25



The title compound was prepared in a similar manner to that mentioned in Example 108, using 4-(2-amino-3-methoxyphenethyl)-2,6-di-tert-butylphenol instead of 4-(2-amino-3,5-difluorophenethyl)-2,6-di-tert-butylphenol.

m.p. 184-185°C

¹H-NMR(δ ppm, CDCl₃) 7.20-7.30(m, 6H), 6.88(d, J=8Hz, 1H), 6.80(s, 2H), 6.77(d, J=8Hz, 1H), 5.07(s, 1H), 4.88(s, 1H), 4.09(d, J=8Hz, 1H), 3.76(s, 3H), 3.60-3.70(m, 1H), 3.43(s, 2H), 2.86-2.90(m, 2H), 2.70-2.77(m, 4H), 2.05(t, J=11Hz, 2H), 1.86(d, J=10Hz, 2H), 1.38(s, 18H), 1.25(q, J=10Hz, 2H)

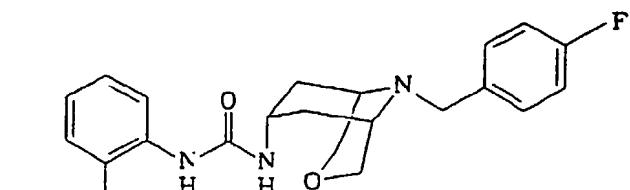
IR(cm⁻¹) 3638, 3308, 1653, 1589, 1563, 1556, 1468, 1454, 1435, 1260, 1232, 738

50 Example 164

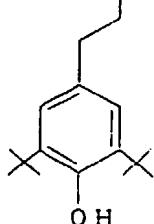
N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-[endo-9-(4-fluorobenzyl)-3-oxa-9-azabicyclo[3.3.1]non-7-yl]urea

55

5



10



15

The title compound was prepared in a similar manner to that mentioned in Example 11, using *endo*-7-amino-9-(4-fluorobenzyl)-3-oxa-9-azabicyclo[3.3.1]nonane instead of decylamine.

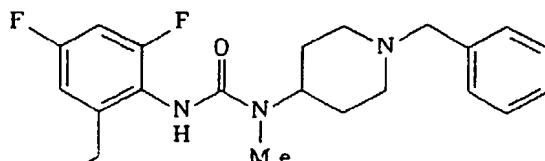
20 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.18-7.29(m, 6H), 7.06(d, $J=11\text{Hz}$, 1H), 6.99(d, $J=9\text{Hz}$, 1H), 6.96(d, $J=9\text{Hz}$, 1H), 6.83(s, 2H), 5.22(s, 1H), 5.09(s, 1H), 4.37(dd, $J=17, 7\text{Hz}$, 1H), 3.73(d, $J=15\text{Hz}$, 2H), 3.71(s, 2H), 3.39(d, $J=11\text{Hz}$, 2H), 2.84-2.87(m, 2H), 2.76-2.79(m, 2H), 2.52(s, 2H), 2.30-2.37(m, 2H), 1.39(s, 18H), 1.31-1.40(m, 2H)

IR(cm^{-1}) 3636, 3324, 1652, 1525, 1511, 1506, 1436, 1223, 787, 759

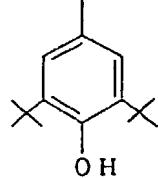
28 Example 165

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]-N'-(1-benzyl-4-piperidyl)-N'-methylurea

30



35



40

The title compound was prepared in a similar manner to that mentioned in Example 108, using 1-benzyl-4-(methylamino)piperidine instead of 4-amino-1-benzylpiperidine. m.p. 187-191°C

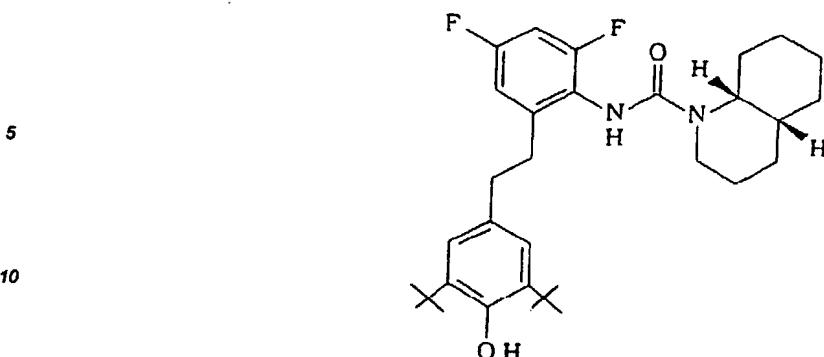
45 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.20-7.40(m, 5H), 6.70-6.80(m, 4H), 5.09(s, 1H), 4.91(bs, 1H), 4.10-4.23(m, 1H), 3.47(s, 2H), 2.90-3.00(m, 2H), 2.80-2.90(m, 4H), 2.58(s, 3H), 2.00-2.10(m, 2H), 1.60-1.80(m, 4H), 1.36(s, 18H)

IR(cm^{-1}) 3616, 3312, 1638, 1510, 1436, 1323, 1118

50 Example 166

2-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]carbamoyl]-cis-decahydroquinoline

55

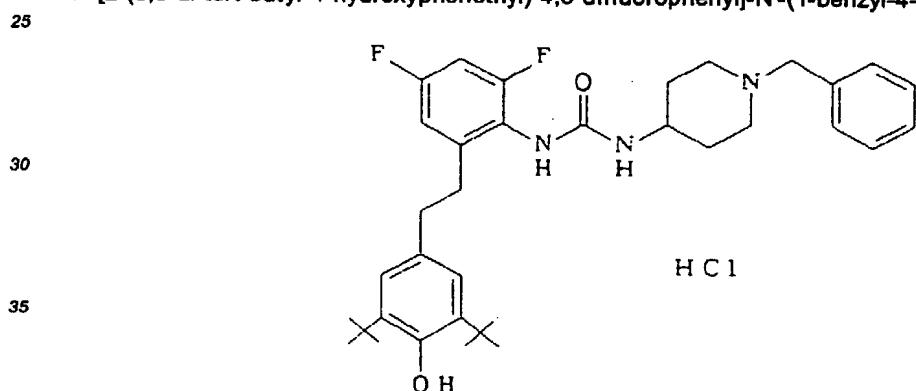


15 The title compound was prepared in a similar manner to that mentioned in Example 108, using *cis*-decahydroquinoline instead of 4-amino-1-benzylpiperidine.
m.p. 83-85°C

20 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 6.83(s, 2H), 6.70-6.80(m, 2H), 5.26(bs, 1H), 5.09(s, 1H), 4.05(bs, 1H), 3.49(bs, 2H), 2.70-2.90(m, 5H), 1.84-1.94(m, 1H), 1.65-1.80(m, 4H), 1.20-1.60(m, 8H), 1.39(s, 18H)
 $\text{IR}(\text{cm}^{-1})$ 3588, 3316, 2924, 1713, 1638, 1511, 1435, 1120

Example 167

25 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]-N'-(1-benzyl-4-piperidyl)urea hydrochloride



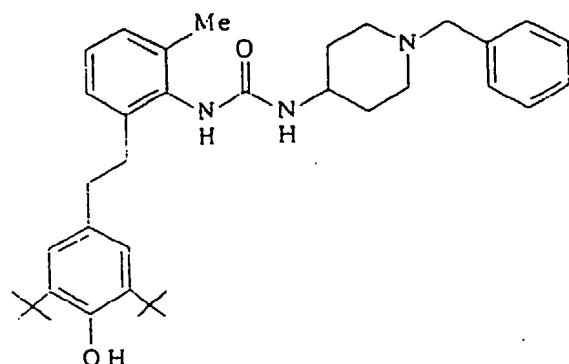
40 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]-N'-(1-benzyl-4-piperidyl)urea (1.15 g) was suspended in ethanol (20 ml) and heated at 50°C to dissolve it. To the solution was added 4N hydrochloric acid/ethyl acetate solution (anhydrous)(0.5 ml). This solution was concentrated to a volume of 5 ml, cooled to 0-5°C and allowed to stand for 4 hrs. The resultant crystals were filtered and dried to afford the title compound (1.00 g, 81%).

45 m.p. 170-175°C

50 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 12.09(bs, 1H), 7.55(d, $J=6\text{Hz}$, 2H), 7.30-7.40(m, 3H), 6.84(s, 2H), 6.72(d, $J=8\text{Hz}$, 1H), 6.65(td, $J=8, 2\text{Hz}$, 1H), 5.10(s, 1H), 4.12(d, $J=7\text{Hz}$, 1H), 3.75-3.86(m, 1H), 3.35-3.40(m, 2H), 2.65-2.85(m, 6H), 2.10-2.25(m, 4H), 1.39(s, 18H)
 $\text{IR}(\text{cm}^{-1})$ 3430, 3300, 2952, 1680, 1554, 1436, 1236, 1122

55 Example 168

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-6-methylphenyl]-N'-(1-benzyl-4-piperidyl)urea



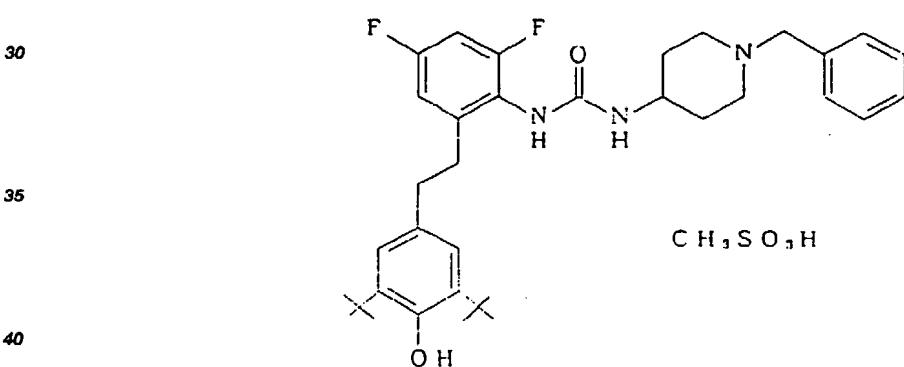
15 The title compound was prepared in a similar manner to that mentioned in Example 108, using 4-(2-amino-3-methylphenethyl)-2,6-di-tert-butylphenol instead of 4-(2-amino-3,5-difluorophenethyl)-2,6-di-tert-butylphenol.
m.p. 185-186°C

20 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.04-7.34(m, 8H), 6.78(s, 2H), 5.08(s, 1H), 4.83(s, 1H), 3.90(d, $J=8\text{Hz}$, 1H), 3.57-3.72(m, 1H), 3.42(s, 2H), 2.62-2.90(m, 6H), 2.19(s, 3H), 2.03(dd, $J=12, 11\text{Hz}$, 2H), 1.83(d, $J=11\text{Hz}$, 2H), 1.38(s, 18H), 1.16-1.32(m, 2H)

IR(cm^{-1}) 3638, 3324, 2950, 1639, 1555, 1436, 1233, 769, 734, 698

Example 169

25 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]-N'-(1-benzyl-4-piperidyl)urea methanesulfonate



45 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]-N'-(1-benzyl-4-piperidyl)urea (0.50 g) was suspended in ethanol (10 ml) and heated at 50°C to dissolve it. To the solution was added methanesulfonic acid (56 μl) and this solution was concentrated. The concentrate was dissolved with a mixed solvent of ethyl acetate (1 ml) and diisopropylether (3 ml). The solution was cooled to 0-5°C and allowed to stand overnight. The resultant crystals were filtered and dried to give the title compound (0.51 g, 87%). m.p. 252-254°C

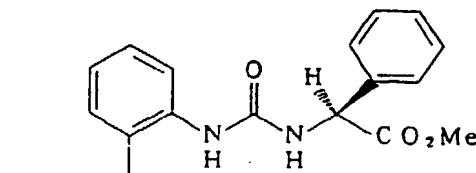
50 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 10.23(bs, 1H), 7.30-7.45(m, 5H), 6.80-6.92(m, 3H), 6.57-6.68(m, 1H), 5.10(s, 1H), 4.30(bs, 1H), 4.12(bs, 1H), 3.74-3.88(m, 1H), 3.40-3.50(m, 2H), 3.20-3.32(m, 1H), 2.60-2.80(m, 9H), 1.90-2.15(m, 4H), 1.39(s, 18H)

IR(cm^{-1}) 3262, 2954, 1657, 1562, 1438, 1220, 1163, 1119, 1041

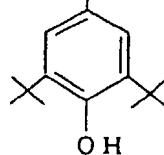
Example 170

55 (S)-N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(α -methoxycarbonyl)benzylurea

5



10



15

The title compound was prepared in a similar manner to that mentioned in Example 11, using (S)- α -phenylglycine methyl ester instead of decylamine.

m.p. 145-150°C

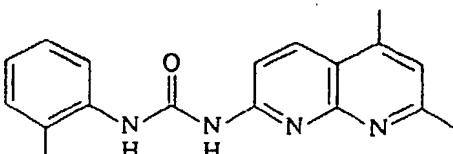
20 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.170-7.34(m, 9H), 6.76(s, 2H), 5.51(d, $J=8\text{Hz}$, 1H), 5.23(d, $J=7\text{Hz}$, 1H), 5.13(s, 1H), 5.09(s, 1H), 3.68(s, 3H), 2.74-2.88(m, 4H), 1.35(s, 18H)
 $\text{IR}(\text{cm}^{-1})$ 3644, 3345, 2944, 1752, 1644, 1546, 1436, 1211

Example 171

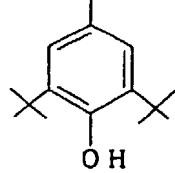
25

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(2,4-dimethyl-1,8-naphthyridin-7-yl)urea

30



35



40

The title compound was prepared in a similar manner to that mentioned in Example 11, using 7-amino-2,4-dimethyl-1,8-naphthyridine instead of decylamine.

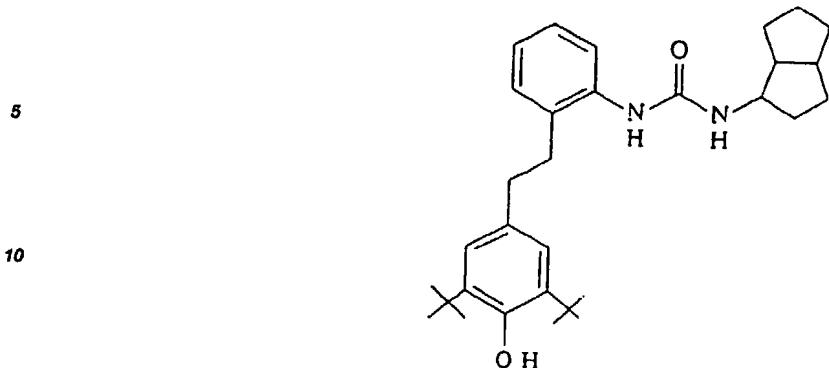
45 m.p. 235-237°C

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 8.22(d, $J=9\text{Hz}$, 1H), 7.86-7.96(m, 1H), 7.10-7.30(m, 3H), 7.02(s, 1H), 6.80(s, 2H), 4.93(s, 1H), 3.15-3.27(m, 2H), 2.90-3.01(m, 2H), 2.62(s, 3H), 2.56(bs, 3H), 1.23(s, 18H)
 $\text{IR}(\text{cm}^{-1})$ 3636, 2952, 1687, 1615, 1599, 1560, 1527, 1403, 1307, 751

50 Example 172

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(bicyclo[3.3.0]-2-octyl)urea

55



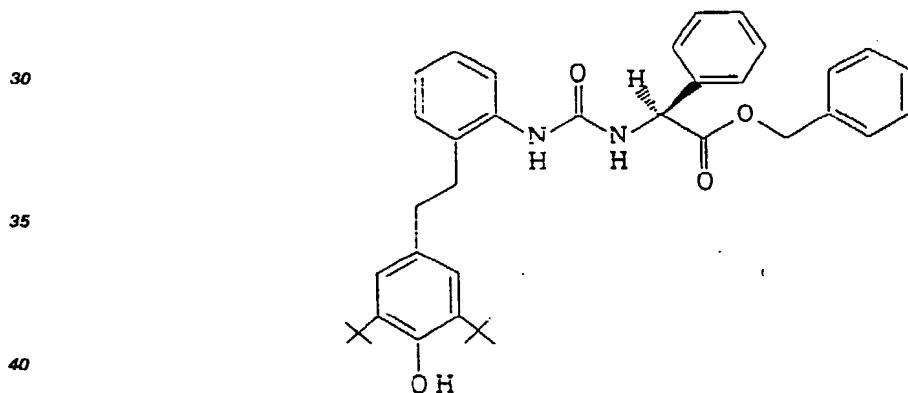
The title compound was prepared in a similar manner to that mentioned in Example 11, using 1-aminobicyclo[3.3.0]octane instead of decylamine.

20 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.14-7.29(m, 4H), 6.80(s, 2H), 5.11(s, 1H), 5.060(s, 1H), 4.15(d, $J=8\text{Hz}$, 1H), 3.62-3.72(m, 1H), 2.75-2.88(m, 4H), 2.34-2.45(m, 1H), 1.87-2.01(m, 2H), 1.72-1.83(m, 1H), 1.43-1.63(m, 4H), 1.38(s, 18H), 1.07-1.31(m, 3H)

IR(cm^{-1}) 3634, 2948, 2864, 1637, 1563, 1434, 1231, 760

Example 173

25 (S)-N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(α -benzyloxycarbonyl)benzylurea



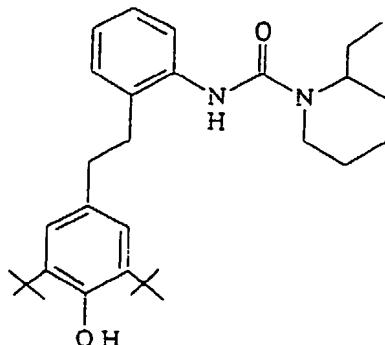
The title compound was prepared in a similar manner to that mentioned in Example 11, using (S)- α -phenylglycine benzyl ester instead of decylamine.

45 m.p. 132-134°C
 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.13-7.33(m, 14H), 6.75(s, 2H), 5.57(d, $J=8\text{Hz}$, 1H), 5.27(d, $J=7\text{Hz}$, 1H), 5.15(s, 1H), 5.11(s, 2H), 5.08(s, 1H), 2.74-2.87(m, 4H), 1.34(s, 18H)
IR(cm^{-1}) 3642, 3344, 2944, 1749, 1643, 1587, 1553, 1168, 749, 697

50 **Example 174**

1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-2-ethylpiperidine

5



10

15 The title compound was prepared in a similar manner to that mentioned in Example 11, using 2-ethylpiperidine instead of decylamine. m.p. 137-138°C

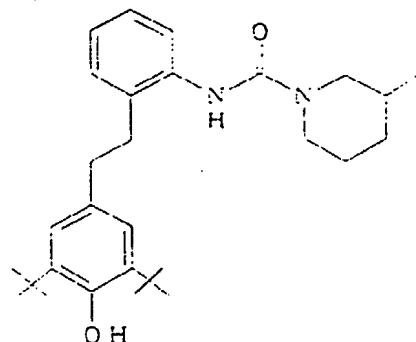
¹H-NMR(δ ppm, CDCl₃) 7.52-7.58(m, 1H), 7.16-7.23(m, 2H), 7.04-7.10(m, 1H), 6.84(s, 2H), 5.78(s, 1H), 5.08(s, 1H), 3.91-4.00(m, 1H), 3.51-3.61(m, 1H), 2.76-2.87(m, 5H), 1.45-1.80(m, 8H), 1.38(s, 18H), 0.86(t, J=7Hz, 3H)

20 IR(cm⁻¹) 3450, 3300, 2960, 1840, 1510, 1490, 1455, 1250, 885, 765

Example 175

25 1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-3-methylpiperidine

30



35

40 The title compound was prepared in a similar manner to that mentioned in Example 11, using 3-methylpiperidine instead of decylamine.

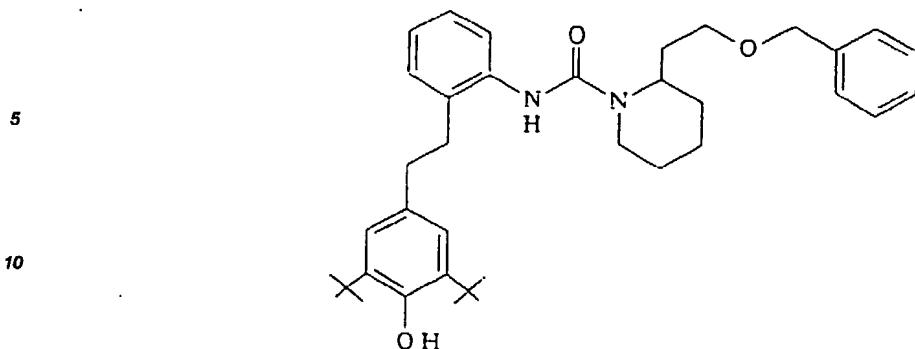
¹H-NMR(δ ppm, CDCl₃) 7.49-7.54(m, 1H), 7.16-7.24(m, 2H), 7.07-7.13(m, 1H), 6.83(s, 2H), 5.72(s, 1H), 5.09(s, 1H), 3.80-3.87(m, 1H), 3.46-3.54(m, 1H), 2.82(s, 4H), 2.70-2.82(m, 2H), 2.35-2.44(m, 1H), 1.76-1.84(m, 1H), 1.40-1.67(m, 3H), 1.38(s, 18H), 1.02-1.14(m, 1H), 0.88(t, J=6Hz, 3H)

45 IR(cm⁻¹) 3645, 3430, 3310, 2960, 2870, 1640, 1525, 1435, 1250, 1150, 750

Example 176

50 1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-2-[2-(benzyloxy)ethyl]piperidine

55

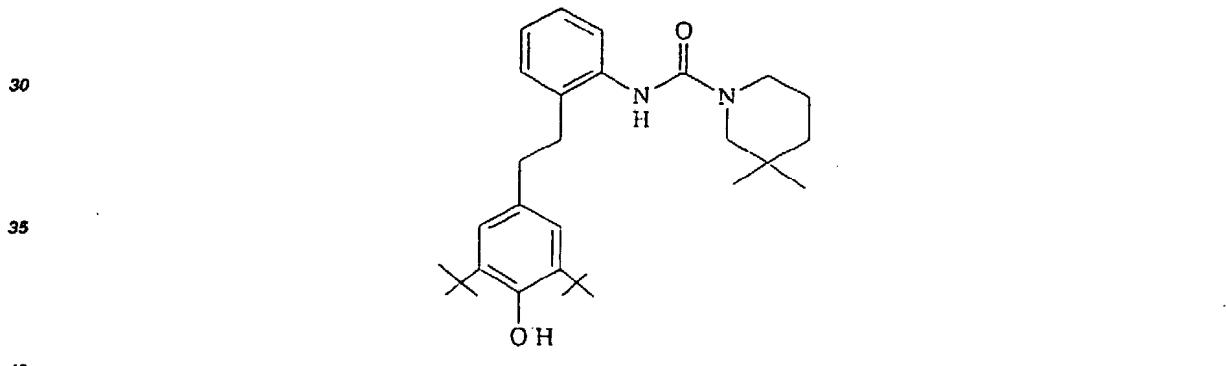


1H-NMR(δ ppm, CDCl_3) 7.53(d, $J=8\text{Hz}$, 1H), 7.02-7.22(m, 8H), 6.89(s, 2H), 6.74(bs, 1H), 5.05(s, 1H), 4.35-4.44(m, 2H), 4.23-4.32(m, 1H), 4.03-4.15(m, 1H), 3.44-3.59(m, 2H), 2.63-2.77(m, 5H), 2.00-2.12(m, 1H), 1.44-1.82(m, 7H), 1.37(s, 18H)

IR(cm^{-1}) 3600, 3420, 2940, 2870, 1665, 1595, 1535, 1450, 1400, 1380, 1270, 1240, 1100, 765, 745

Example 177

25 1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-3,3-dimethylpiperidine



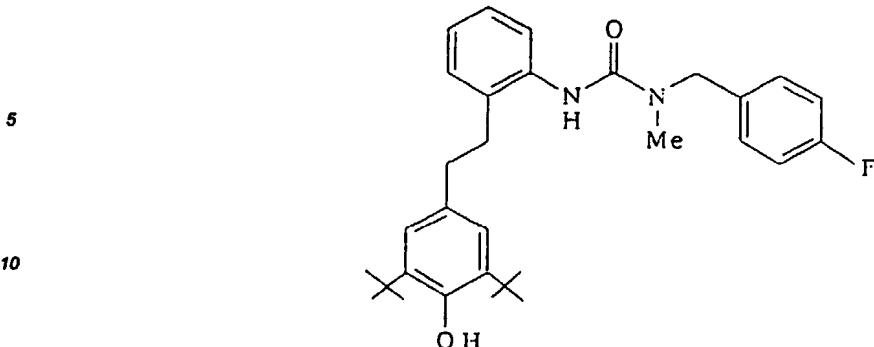
1H-NMR(δ ppm, CDCl_3) 7.54(dd, $J=8, 1\text{Hz}$, 1H), 7.16-7.23(m, 2H), 7.04-7.12(m, 1H), 6.84(s, 2H), 5.77(s, 1H), 5.08(s, 1H), 3.19(t, $J=6\text{Hz}$, 2H), 3.05(s, 2H), 2.82(s, 4H), 1.52-1.61(m, 2H), 1.33-1.43(m, 2H), 1.39(s, 18H), 0.92(s, 6H)

IR(cm^{-1}) 3645, 3430, 3320, 2960, 2870, 1640, 1520, 1440, 1250, 1165, 755

Example 178

50 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(4-fluorobenzyl)-N'-methylurea

55



15 The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-fluoro-N-methylphenethylamine instead of decylamine.

¹H-NMR(δ ppm, CDCl₃) 7.63(d, J=8Hz, 1H), 7.17-7.26(m, 4H), 7.11(dd, J=8, 7Hz, 1H), 6.97(dd, J=9, 9Hz, 2H), 6.75(s, 2H), 5.66(s, 1H), 5.06(s, 1H), 4.45(s, 2H), 2.73-2.84(m, 4H), 2.64(s, 3H), 1.33(s, 18H)
IR(cm⁻¹) 3645, 3430, 3320, 2965, 1650, 1515, 1440, 1380, 1300, 1230, 1160, 760

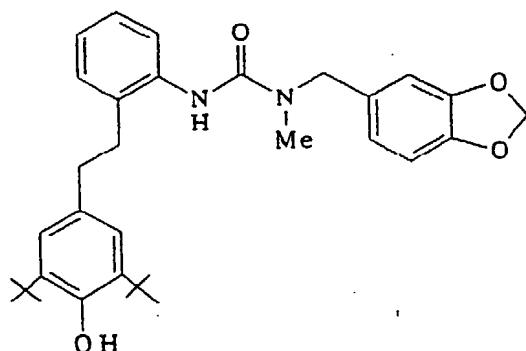
20

Example 179

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]-N'-(3,4-methylenedioxybenzyl)-N'-methylurea

25

30



40 The title compound was prepared in a similar manner to that mentioned in Example 11, using 5-(methylaminomethyl)-1,3-dioxindane instead of decylamine.

m.p. 152-153°C

¹H-NMR(δ ppm, CDCl₃) 7.65(d, J=8Hz, 1H), 7.16-7.25(m, 2H), 7.10(dd, J=7, 7Hz, 1H), 6.76(s, 2H), 6.65-6.73(m, 2H), 5.92(s, 2H), 5.69(s, 1H), 5.06(s, 1H), 4.39(s, 2H), 2.72-2.83(m, 4H), 2.66(s, 3H), 1.34(s, 18H)

45

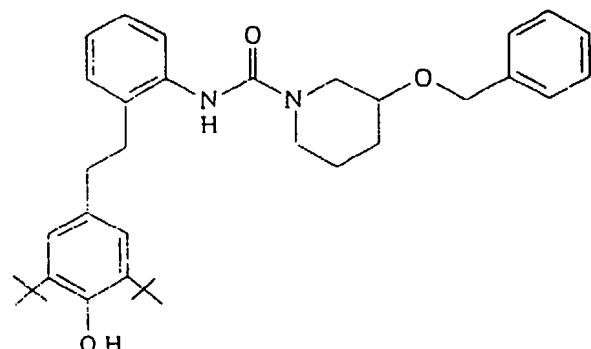
Example 180

1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-3-(benzyloxy)piperidine

50

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5



10

15 The title compound was prepared in a similar manner to that mentioned in Example 11, using 3-benzyloxypiperidine instead of decylamine.

¹H-NMR(δ ppm, CDCl₃) 7.44(d, J=8Hz, 1H), 7.22-7.34(m, 5H), 7.18(dd, J=7, 7Hz, 1H), 7.08(dd, J=7, 7Hz, 1H), 6.80(s, 2H), 5.82(s, 1H), 5.06(s, 1H), 4.47-4.56(m, 2H), 3.68-3.76(m, 1H), 3.43-3.51(m, 1H), 3.09-3.22(m, 3H), 2.71-2.83(m, 4H), 1.61-1.96(m, 3H), 1.38-1.50(m, 1H), 1.36(s, 18H)

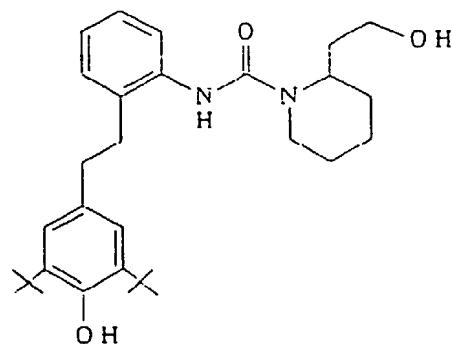
20 IR(cm⁻¹) 3625, 3280, 2960, 1635, 1525, 1490, 1445, 1245, 1045, 940, 765

Example 181

25 1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-2-(2-hydroxyethyl)piperidine

26

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The title compound was prepared in a similar manner to that mentioned in Example 11, using 2-(2-hydroxyethyl)piperidine instead of decylamine.

¹H-NMR(δ ppm, CDCl₃) 7.46(d, J=8Hz, 1H), 7.16-7.24(m, 2H), 7.11(dd, J=8, 7, 1Hz, 1H), 6.84(s, 2H), 6.00-6.21(br, 1H), 5.08(s, 1H), 4.51-4.62(m, 1H), 3.57-3.66(m, 1H), 3.48-3.18(m, 3H), 2.69-2.88(m, 5H), 1.40-2.03(m, 8H), 1.38(s, 18H)

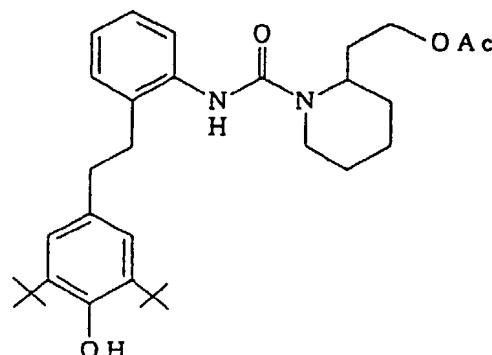
45 IR(cm⁻¹) 3640, 3320, 2950, 2870, 1640, 1530, 1440, 1275, 1230, 1175, 755

Example 182

50 1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-2-(2-acetoxyethyl)piperidine

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15 The title compound was prepared in a similar manner to that mentioned in Example 11, using 2-(2-acetoxyethyl)piperidine instead of decylamine.

¹H-NMR(δ ppm, CDCl₃) 7.49(d, J=8Hz, 1H), 7.17-7.23(m, 2H), 7.09(d, J=7Hz, 1H), 6.84(s, 2H), 5.84(s, 1H), 5.08(s, 1H), 4.33-4.43(m, 1H), 4.00-4.16(m, 2H), 3.41-3.51(m, 1H), 2.76-2.90(m, 5H), 2.00-2.12(m, 1H), 1.97(s, 3H), 1.74-1.85(m, 1H), 1.38-1.72(m, 6H), 1.38(s, 18H)

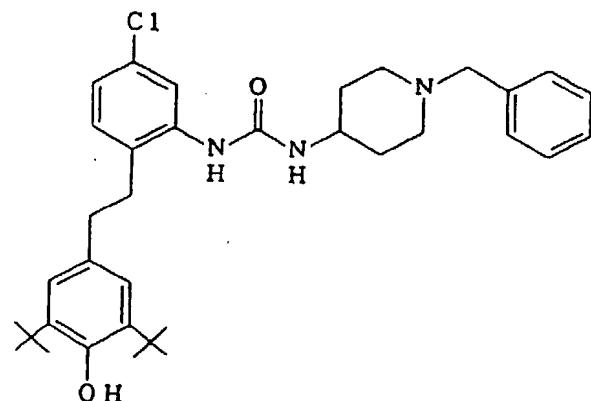
20 IR(cm⁻¹) 3640, 3425, 2960, 2870, 1740, 1640, 1520, 1435, 1370, 1235, 750

Example 183

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-5-chlorophenyl]-N'-(1-benzyl-4-piperidyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 108, using 4-(2-amino-4-chlorophenethyl)-2,6-di-tert-butylphenol instead of 4-(2-amino-3,5-difluorophenethyl)-2,6-di-tert-butylphenol.

45 m.p. 155-156°C

¹H-NMR(δ ppm, CDCl₃) 7.41(s, 1H), 7.22-7.31(m, 5H), 7.08(s, 2H), 6.77(s, 2H), 5.22(s, 1H), 5.12(s, 1H), 4.20(d, J=8Hz, 1H), 3.45-3.65(m, 1H), 3.45(s, 2H), 2.75(s, 4H), 2.73-2.77(m, 2H), 2.04(t, J=11Hz, 2H), 1.85(d, J=11Hz, 2H), 1.38(s, 18H), 1.22-1.42(m, 2H)

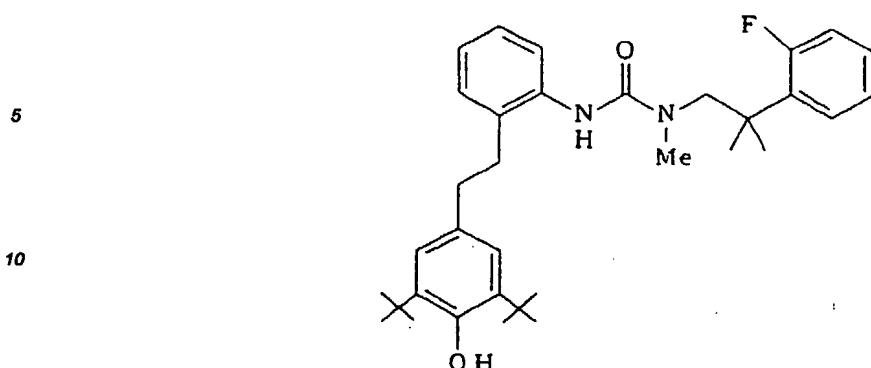
IR(cm⁻¹) 3645, 3370, 1633, 1545, 1438, 1234, 699

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Example 184

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-5-chlorophenyl]-N'-(2-(2-fluorophenyl)-2-methylpropyl)-N'-methylurea

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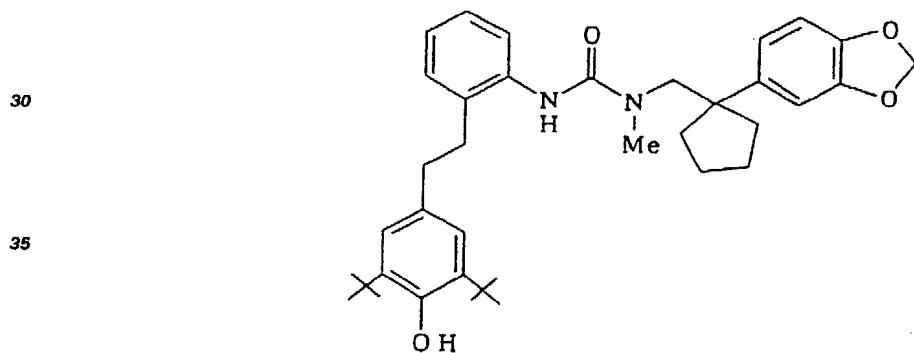


The title compound was prepared in a similar manner to that mentioned in Example 11, using 2-fluoro- β,β -dimethylphenethylamine instead of decylamine.

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.53(d, $J=8\text{Hz}$, 1H), 7.17-7.28(m, 4H), 7.05-7.14(m, 2H), 6.94-7.03(m, 1H), 6.73(s, 2H), 5.49(s, 1H), 5.01(s, 1H), 3.70(s, 2H), 2.73-2.83(m, 4H), 2.21(s, 3H), 1.37(s, 6H), 1.29(s, 18H)
 20 $\text{IR}(\text{cm}^{-1})$ 3640, 3430, 2965, 1660, 1510, 1490, 1440, 1210, 760

Example 185

25 **N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-5-chlorophenyl]-N'-methyl-N-[1-(3,4-methylenedioxyphenyl)cyclo-
 penty] methylurea**



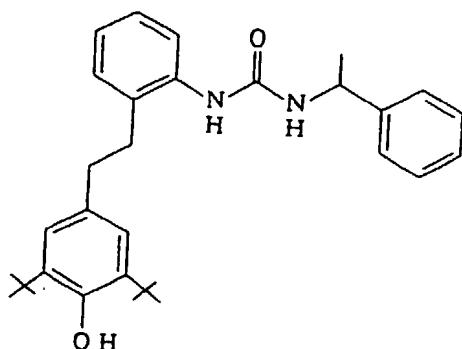
The title compound was prepared in a similar manner to that mentioned in Example 11, using 5-[1-(N-methylaminomethyl)cyclopentyl]-1,3-dioxane instead of decylamine.

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.45(d, $J=7\text{Hz}$, 1H), 7.16-7.24(m, 2H), 7.06-7.13(m, 1H), 6.78(s, 1H), 6.72(s, 4H), 5.92(s, 2H), 5.32(s, 1H), 5.03(s, 1H), 3.42(s, 2H), 2.73-2.82(s, 4H), 2.02(s, 3H), 2.58-2.98(m, 8H), 1.30(s, 18H)
 45 $\text{IR}(\text{cm}^{-1})$ 3640, 3430, 2960, 1660, 1510, 1490, 1435, 1235, 1450, 760

Example 186

50 **N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-5-chlorophenyl]-N'-(α -methylbenzyl)urea**

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The title compound was prepared in a similar manner to that mentioned in Example 11, using α -methylbenzylamine instead of decylamine. m.p. 167-168°C

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.12-7.33(m, 9H), 6.77(s, 2H), 5.15(s, 1H), 5.09(s, 1H), 4.96(dq, $J=7, 7\text{Hz}$, 1H), 4.53(d, $J=7\text{Hz}$, 1H), 2.70-2.82(m, 4H), 1.40(d, $J=7\text{Hz}$, 3H), 1.37(s, 18H)
 $\text{IR(cm}^{-1}\text{)} 3625, 3320, 3275, 2960, 1630, 1565, 1435, 1235, 745, 700$

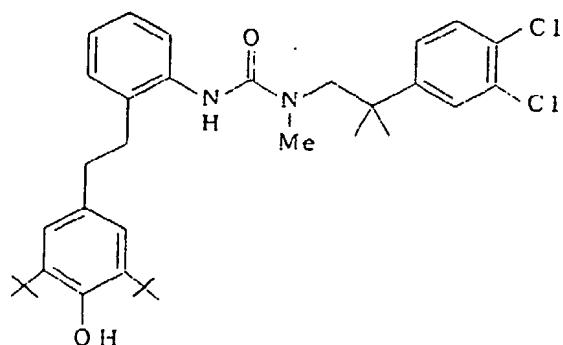
20

Example 187

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-5-chlorophenyl]-N'-(2-(3,4-dichlorophenyl)-2-methylpropyl)-N-methylurea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using N-methyl-3,4-dichloro- β,β -dimethylphenethylamine instead of decylamine.

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.48(d, $J=8\text{Hz}$, 1H), 7.43(d, $J=2\text{Hz}$, 1H), 7.37(d, $J=10\text{Hz}$, 1H), 7.17-7.27(m, 3H), 7.09-7.15(m, 1H), 6.71(s, 2H), 5.38(s, 1H), 5.08(s, 1H), 3.48(s, 2H), 2.72-2.84(m, 4H), 2.13(s, 3H), 1.36(s, 6H), 1.29(s, 18H)
 $\text{IR(cm}^{-1}\text{)} 3640, 3430, 3330, 2970, 1660, 1515, 1480, 1450, 1440, 1310, 1250, 1030, 880, 760$

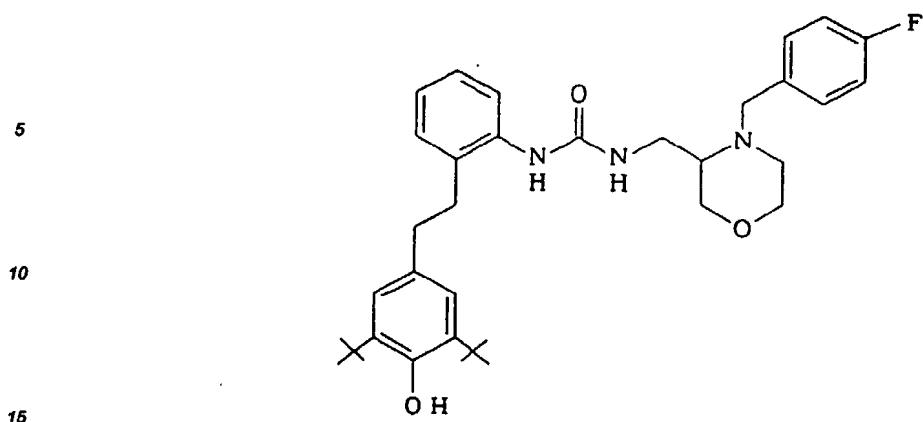
45

Example 188

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N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-5-chlorophenyl]-N'-(4-(4-fluorobenzyl)-3-morpholinylmethylurea

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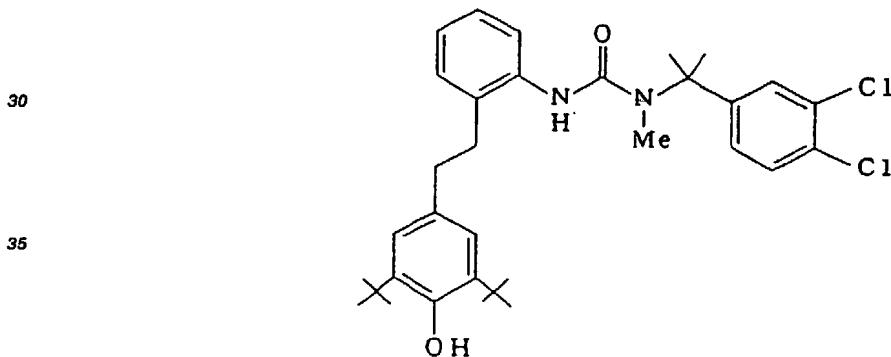


The title compound was prepared in a similar manner to that mentioned in Example 11, using 3-methylamino-4-(4-fluorobenzyl)morpholine instead of decylamine.

20 $^1\text{H-NMR}(\delta \text{ ppm, CDCl}_3)$ 7.19-7.37(m, 4H), 6.80-6.89(m, 4H), 6.76(s, 2H), 5.11(s, 1H), 5.05(s, 1H), 4.96(bs, 1H), 3.89(d, $J=13\text{Hz}$, 1H), 3.74(dd, $J=12, 3\text{Hz}$, 1H), 3.64(d, $J=12\text{Hz}$, 1H), 3.31-3.42(m, 4H), 3.03(d, $J=13\text{Hz}$, 1H), 2.70-2.88(m, 4H), 2.48-2.56(m, 1H), 2.45(d, $J=12\text{Hz}$, 1H), 2.10(dt, $J=11, 3\text{Hz}$, 1H), 1.37(s, 18H)

Example 189

25 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-5-chlorophenyl]-N'-(2-(3,4-dichlorophenyl)-2-propyl)-N'-methylurea



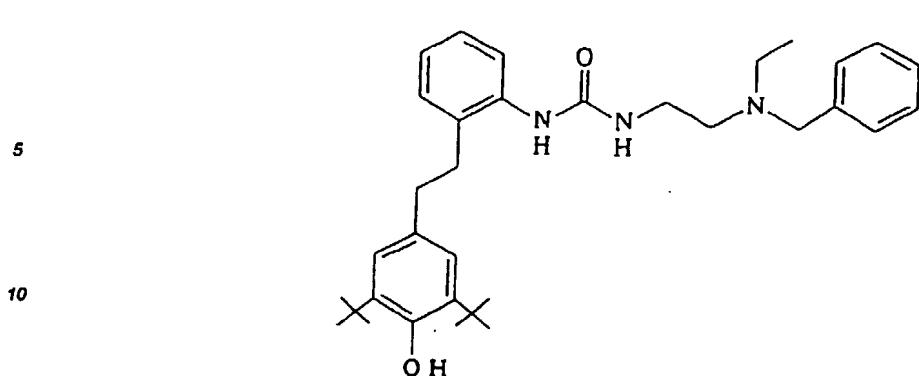
The title compound was prepared in a similar manner to that mentioned in Example 11, using 3,4-dichloro-N, α , α -trimethylbenzylamine instead of decylamine.

45 $^1\text{H-NMR}(\delta \text{ ppm, CDCl}_3)$ 7.36-7.42(m, 2H), 7.24-7.29(m, 1H), 7.09-7.17(m, 3H), 7.02-7.07(m, 1H), 6.79(s, 2H), 5.52(s, 1H), 5.09(s, 1H), 2.81(s, 3H), 2.61-2.78(m, 4H), 1.63(s, 6H), 1.38(s, 18H)
 IR(cm^{-1}) 3640, 3290, 2960, 2875, 1640, 1520, 1485, 1440, 1340, 1245, 1140, 1030, 755

Example 190

50 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-5-chlorophenyl]-N'-(2-(N-benzyl-N-ethylamino)ethyl)urea

55



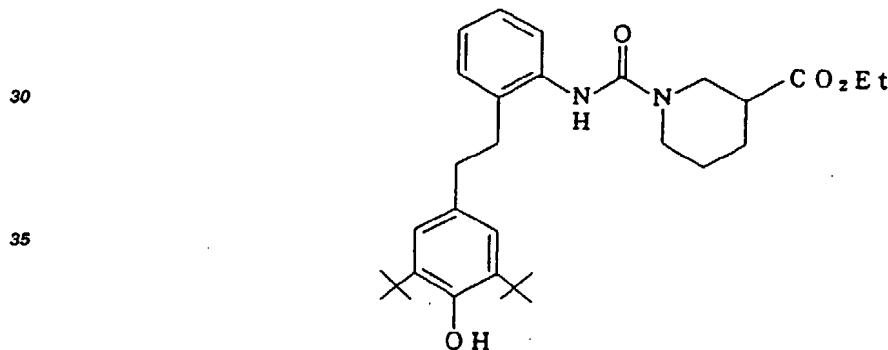
m.p. 132-133°C

18 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.16-7.36(m, 7H), 6.92-6.98(m, 2H), 6.79(s, 2H), 5.12(bs, 1H), 5.09(s, 1H), 5.00-5.05(m, 1H), 3.43(s, 2H), 3.21(td, $J=6, 5\text{Hz}$, 2H), 2.74-2.90(m, 4H), 2.46(t, $J=6\text{Hz}$, 2H), 2.37(q, $J=7\text{Hz}$, 2H), 1.38(s, 18H), 0.87(t, $J=7\text{Hz}$, 3H)

20 $\text{IR(cm}^{-1}\text{)}$ 3650, 3340, 3280, 2960, 2810, 1640, 1585, 1560, 1440, 1235, 1150, 865, 745, 705

Example 191

25 1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)phenyl]carbamoyl]-3-ethoxycarbonylpiperidine



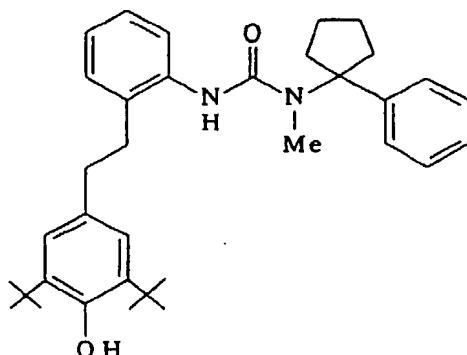
43 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.53(d, $J=8\text{Hz}$, 1H), 7.15-7.22(m, 2H), 7.04-7.09(m, 1H), 6.84(s, 2H), 6.30(s, 1H), 5.07(s, 1H), 4.06-4.15(m, 2H), 3.74-3.81(m, 1H), 3.30-3.42(m, 2H), 3.10-3.17(m, 1H), 2.78-2.92(m, 4H), 2.52-2.59(m, 1H), 1.83-2.00(m, 2H), 1.46-1.66(m, 2H), 1.38(s, 18H), 1.22(t, $J=7\text{Hz}$, 3H)

45 $\text{IR(cm}^{-1}\text{)}$ 3425, 2945, 2870, 1725, 1650, 1595, 1530, 1450, 1375, 1300, 1210, 1030, 885, 760

Example 192

50 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-5-chlorophenyl]-N'-(1-phenylcyclopentyl)-N'-methylurea

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The title compound was prepared in a similar manner to that mentioned in Example 11, using N-methyl-1-phenylcyclopentylamine instead of decylamine.

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.47(d, $J=8\text{Hz}$, 1H), 7.33(dd, $J=8, 1\text{Hz}$, 1H), 7.08-7.18(m, 3H), 6.93-7.02(m, 3H), 6.78(s, 2H), 5.75(s, 1H), 5.07(s, 1H), 3.15(s, 3H), 2.57(t, $J=8\text{Hz}$, 2H), 2.23-2.39(m, 4H), 2.20(t, $J=8\text{Hz}$, 2H), 1.64-1.85(m, 4H), 1.42(s, 18H)

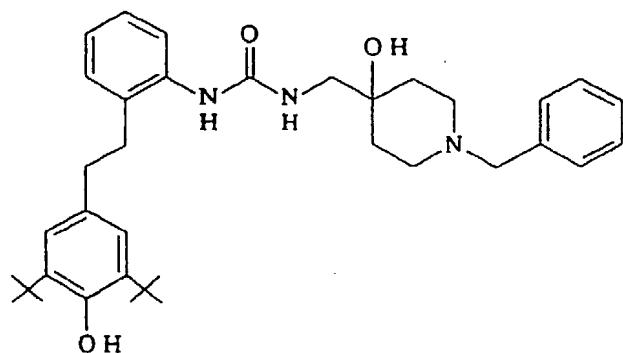
20 $\text{IR}(\text{cm}^{-1})$ 3630, 3410, 2950, 1640, 1520, 1440, 1345, 1230, 755, 700

Example 193

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N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-5-chlorophenyl]-N'-(1-benzyl-4-hydroxy-4-piperidyl)methylurea

30



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40

The title compound was prepared in a similar manner to that mentioned in Example 11, using 4-amino-1-benzyl-4-hydroxypiperidine instead of decylamine.

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.15-7.35(m, 9H), 6.76(s, 2H), 5.12(s, 1H), 5.08(bs, 1H), 4.56(t, $J=5\text{Hz}$, 1H), 3.51(s, 2H), 3.37(bs, 1H), 3.14(d, $J=5\text{Hz}$, 2H), 2.70-2.85(m, 4H), 2.50-2.60(m, 2H), 2.30-2.40(m, 2H), 1.45-1.60(m, 4H), 1.36(s, 18H)

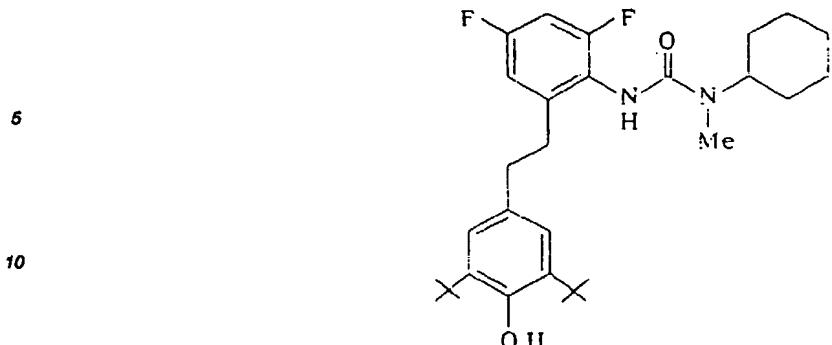
45 $\text{IR}(\text{cm}^{-1})$ 3350, 2952, 1639, 1550, 1435, 1234, 741, 699

Example 194

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N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]-N'-cyclohexyl-N'-methylurea

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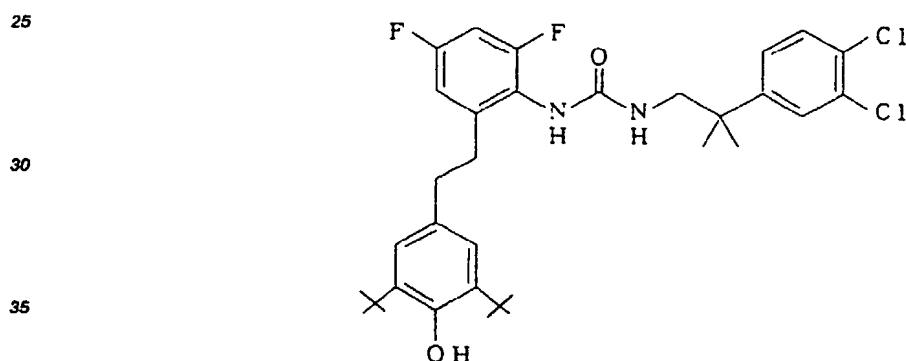


15 The title compound was prepared in a similar manner to that mentioned in Example 108, using N-methylcyclohexylamine instead of 4-amino-1-benzylpiperidine.

1H-NMR(δ ppm, CDCl_3) 6.70-6.80(m, 2H), 6.79(s, 2H), 5.09(s, 1H), 4.98(bs, 1H), 4.00-4.10(m, 1H), 2.75-2.90(m, 4H), 2.60(s, 3H), 1.60-1.80(m, 4H), 1.20-1.50(m, 24H)
 IR(cm^{-1}) 3630, 3420, 2930, 1639, 1499, 1435, 1317, 1237, 1119

20 Example 195

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]-N'-(2-(3,4-dichlorophenyl)-2-methylpropyl)urea



40 The title compound was prepared in a similar manner to that mentioned in Example 108, using 3,4-dichloro- β,β -dimethylphenethylamine instead of 4-amino-1-benzylpiperidine. m.p. 159-160°C

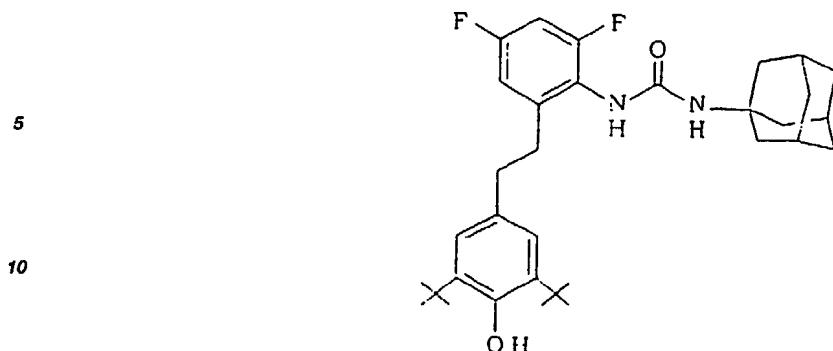
1H-NMR(δ ppm, CDCl_3) 7.05-7.30(m, 3H), 6.65-6.78(m, 4H), 5.08-5.11(m, 1H), 4.27(bs, 1H), 3.72(bt, $J=6\text{Hz}$, 1H), 3.28-3.31(m, 2H), 2.65-2.80(m, 4H), 1.30-1.40(m, 18H), 1.20-1.30(m, 6H)
 IR(cm^{-1}) 3640, 3310, 2958, 1638, 1566, 1436, 1235, 1118

45 Example 196

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]-N'-(1-adamantyl)urea

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The title compound was prepared in a similar manner to that mentioned in Example 108, using 1-adamantanamine instead of 4-amino-1-benzylpiperidine.

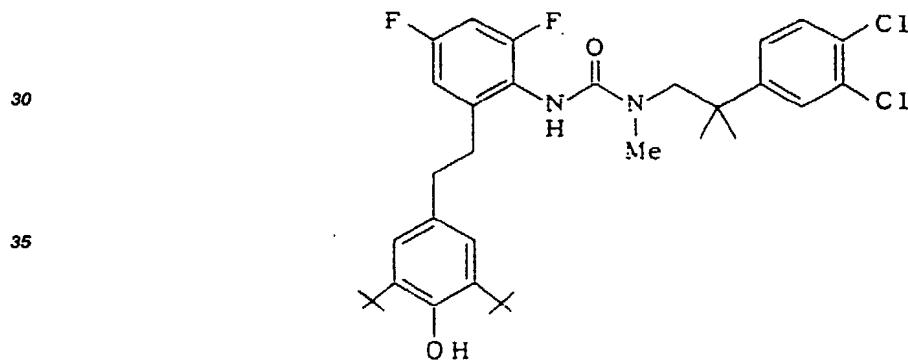
m.p. 218-220°C

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 6.81(s, 2H), 6.70-6.80(m, 2H), 5.12(s, 1H), 4.60(bs, 1H), 3.93(bs, 1H), 2.88(t, $J=7\text{Hz}$, 2H), 2.78(t, $J=7\text{Hz}$, 2H), 2.03(bs, 3H), 1.91(d, $J=3\text{Hz}$, 6H), 1.64(bs, 6H), 1.40(s, 18H)

IR(cm^{-1}) 3642, 3375, 2910, 1650, 1562, 1495, 1436, 1235, 1120

Example 197

N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]-N'-(2-(3,4-dichlorophenyl)-2-methylpropyl)-N'-methylurea



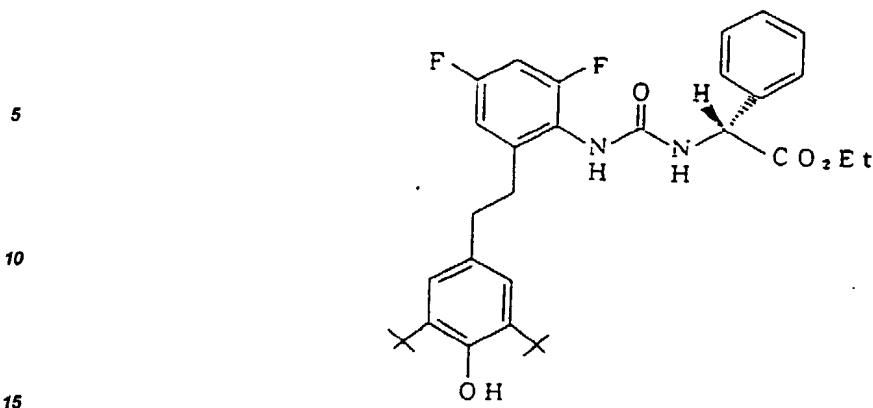
The title compound was prepared in a similar manner to that mentioned in Example 108, using N-methyl-3,4-dichloro- β,β -dimethylphenethylamine instead of 4-amino-1-benzylpiperidine. m.p. 145-147°C

$^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.15-7.40(m, 3H), 6.65-6.80(m, 4H), 5.04-5.06(m, 1H), 4.70-4.73(m, 1H), 3.46-3.49(m, 2H), 2.75-2.85(m, 4H), 2.20-2.24(m, 3H), 1.30-1.34(m, 24H)

IR(cm^{-1}) 3572, 3420, 2954, 1665, 1505, 1434, 1120

Example 198

(R)-N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]-N'-(α -ethoxycarbonylbenzyl)urea

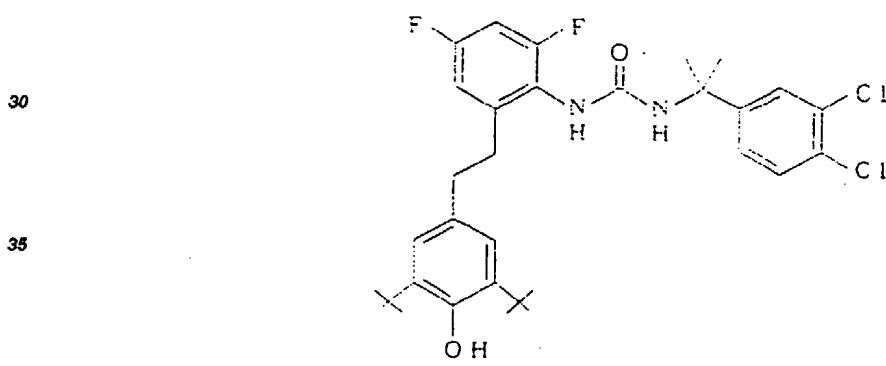


The title compound was prepared in a similar manner to that mentioned in Example 108, using (R)- α -phenylglycine ethyl ester instead of 4-amino-1-benzylpiperidine. m.p. 162-164°C

20 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.26-7.32(m, 5H), 6.73-6.80(m, 4H), 5.45(d, $J=7\text{Hz}$, 1H), 5.22(bd, $J=7\text{Hz}$, 1H), 5.12(s, 1H), 4.68(bs, 1H), 4.08-4.20(m, 2H), 2.72-2.89(m, 4H), 1.37(s, 18H), 1.18(t, $J=7\text{Hz}$, 3H)
 IR(cm^{-1}) 3640, 3350, 2956, 1737, 1641, 1561, 1438, 1122

Example 199

25 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]-N'-[2-(3,4-dichlorophenyl)-2-propyl]urea



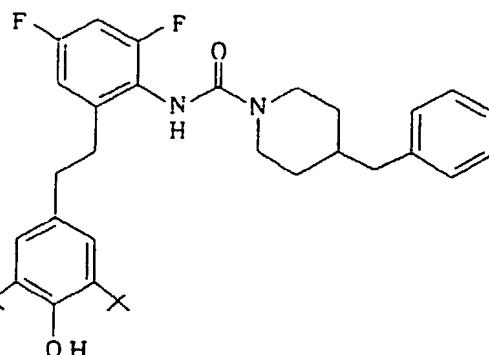
The title compound was prepared in a similar manner to that mentioned in Example 108, using 3,4-dichloro- α,α -dimethylbenzylamine instead of 4-amino-1-benzylpiperidine. m.p. 224-226°C

45 $^1\text{H-NMR}$ (δ ppm, CDCl_3) 7.42(d, $J=2\text{Hz}$, 1H), 7.31(d, $J=9\text{Hz}$, 1H), 7.18(dd, $J=9, 2\text{Hz}$, 1H), 6.75-6.80(m, 4H), 5.13(s, 1H), 4.62(bs, 1H), 4.53(bs, 1H), 2.56(t, $J=7\text{Hz}$, 2H), 2.77(t, $J=7\text{Hz}$, 2H), 1.57(s, 6H), 1.40(s, 18H)
 IR(cm^{-1}) 3634, 3354, 2954, 1649, 1562, 1435, 1277, 1238, 1122

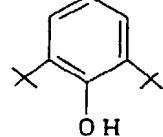
Example 200

50 1-[N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]carbamoyl]-4-benzylpiperidine

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15 The title compound was prepared in a similar manner to that mentioned in Example 108, using 4-benzylpiperidine instead of 4-amino-1-benzylpiperidine.

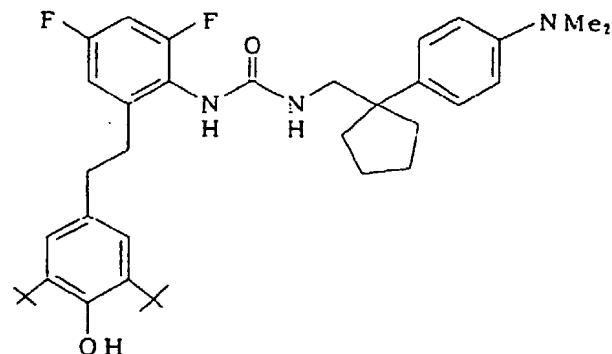
1H-NMR(δ ppm, CDCl_3) 7.25-7.31(m, 2H), 7.20(t, $J=7\text{Hz}$, 1H), 7.12(d, $J=7\text{Hz}$, 2H), 6.71-6.80(m, 2H), 6.75(s, 2H), 5.09(s, 1H), 4.96(s, 1H), 3.73(bd, $J=13\text{Hz}$, 2H), 2.78-2.85(m, 4H), 2.67(t, $J=12\text{Hz}$, 2H), 2.53(d, $J=7\text{Hz}$, 2H), 1.58-1.71(m, 3H), 1.36(s, 18H), 1.12-1.22(m, 2H)

20 IR(cm^{-1}) 3636, 3418, 3026, 1627, 1499, 1435, 1235, 1120, 789, 748, 700

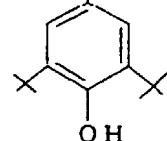
Example 201

25 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]-N'-(1-(4-dimethylaminophenyl)cyclopentyl)methylurea

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The title compound was prepared in a similar manner to that mentioned in Example 108, using 4-[(1-aminomethyl)-1-cyclopentyl]-N,N-dimethylaniline instead of 4-amino-1-benzylpiperidine. m.p. 165-166°C

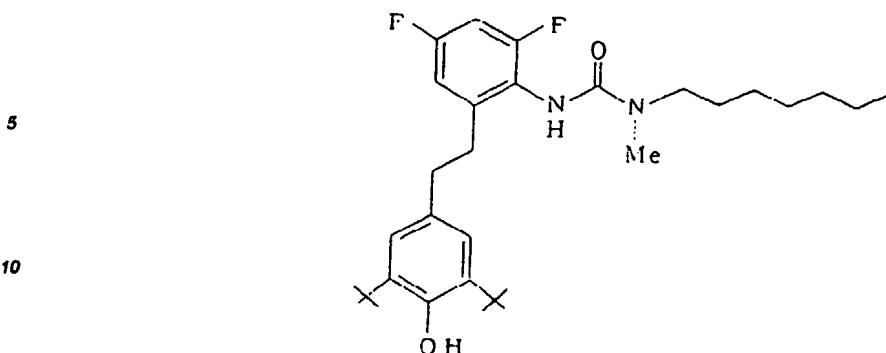
1H-NMR(δ ppm, CDCl_3) 6.92(d, $J=9\text{Hz}$, 2H), 6.75(s, 2H), 6.68-6.76(m, 2H), 6.54(d, $J=9\text{Hz}$, 2H), 5.08(s, 1H), 4.59(s, 1H), 3.82(bs, 1H), 3.19(d, $J=6\text{Hz}$, 2H), 2.89(s, 6H), 2.76(t, $J=7\text{Hz}$, 2H), 2.67(t, $J=7\text{Hz}$, 2H), 1.67-1.90(m, 8H), 1.37(s, 18H)

IR(cm^{-1}) 3674, 3250, 1615, 1520, 1435, 1233, 1121

Example 202

50 N-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]-N'-heptyl-N'-methylurea

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15 The title compound was prepared in a similar manner to that mentioned in Example 108, using N-methylheptylamine instead of 4-amino-1-benzylpiperidine.

¹H-NMR(δ ppm, CDCl₃) 6.70-6.80(m, 2H), 6.77(s, 2H), 5.10(s, 1H), 4.96(s, 1H), 3.21(t, J=8Hz, 2H), 2.75-2.86(m, 4H), 2.75(s, 3H), 1.42-1.56(m, 2H), 1.37(s, 18H), 1.20-1.35(m, 8H), 0.87(t, J=7Hz, 3H)
IR(cm⁻¹) 3640, 3300, 1638, 1503, 1435, 1236, 1120

20 The preparation of the compound of formula (II) used in each of the above examples is illustrated by the following reference examples.

Reference Example 1

25 4-(2-Aminophenethyl)-2,6-di-tert-butylphenol
(1) 2,6-di-tert-Butyl-4-(2-nitrostyryl)phenol



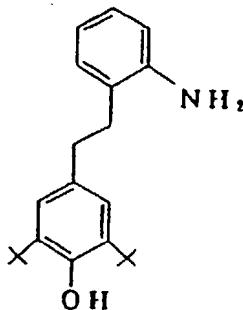
45 To a solution of 3,5-di-tert-butyl-4-hydroxybenzaldehyde (8.09 g, 34.5 mmol) and 2-nitrophenylacetic acid (9.40 g, 51.9 mmol) in xylene (60 ml) was added piperidine (0.3 ml) and the mixture was heated under reflux for 26 hrs while removing water producing with the progress of reaction. After allowing to stand overnight, hexane was added to afford as crystals 2,6-di-tert-butyl-4-(2-nitrostyryl)phenol (7.67 g, 62.9%).

1¹H-NMR (δ ppm, CDCl₃) 7.94(dd, J=8, 1Hz, 1H), 7.76(d, J=8Hz, 1H), 7.57(dd, J=8, 8Hz, 1H), 7.44(d, J=16Hz, 1H), 7.33-7.37(m, 3H), 7.07(d, J=16Hz, 1H), 5.38(s, 1H), 1.48(s, 18H)
(2) 4-(2-Aminophenethyl)-2,6-di-tert-butylphenol

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To a suspension of 2,6-di-tert-butyl-4-(2-nitrostyryl)phenol (16.4 g, 23.3 mmol) in ethanol (150 ml) was added a catalytic amount of 10% palladium carbon and the suspension was subjected to catalytic reduction at room temperature at 1-2.5 atms for 8 hrs and at 40°C for 3 hrs. After filtering the catalyst, distilling off the solvent gave 4-(2-aminophenethyl)-2,6-di-tert-butylphenol (15.1 g, 100%) as a viscous oil.

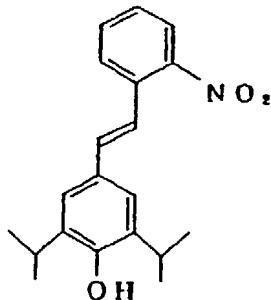
¹H-NMR (δ ppm, CDCl₃) 7.02-7.07(m, 2H), 6.94(s, 2H), 6.74-6.78(m, 1H), 6.67(d, J=8Hz, 1H), 5.06(s, 1H), 3.3-3.7(bs, 2H), 2.73-2.87(m, 4H), 1.41(s, 18H)

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Reference Example 2

(1) 2,6-Diisopropyl-4-(2-nitrostyryl)phenol

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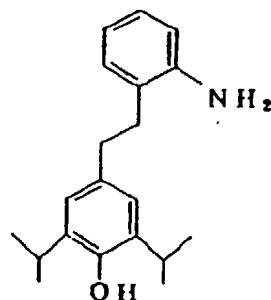
To a solution of 3,5-diisopropyl-4-hydroxybenzaldehyde (0.95 g, 4.6 mmol) and 2-nitrophenyl acetic acid (1.1 g, 6.2 mmol) in xylene (10 ml) was added piperidine (0.05 ml) and the mixture was heated under reflux for 8 hrs while removing water producing with the progress of reaction. After distilling off the solvent followed by purification of the residue by a silica gel column chromatography, recrystallization from hexane gave 2,6-diisopropyl-4-(2-nitrostyryl)phenol (1.3 g, 87%) as crystals.

¹H-NMR (δ ppm, CDCl₃) 7.93-7.95(m, 1H), 7.75-7.77(m, 1H), 7.55-7.57(m, 1H), 7.45(d, J=16Hz, 1H), 7.34-7.38(m, 1H), 7.24(s, 2H), 7.07(d, J=16Hz, 1H), 4.95(s, 1H), 3.12-3.22(m, 2H), 1.32(s, 6H), 1.30(s, 6H)

45

(2) 4-(2-Aminophenethyl)-2,6-diisopropylphenol

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To a suspension of 2,6-diisopropyl-4-(2-nitrostyryl)phenol (1.3 g, 4.0 mmol) in ethanol (20 ml) was added a catalytic amount of 10% palladium carbon and the suspension was subjected to catalytic reduction at 1-2.5 atms at room temperature for 7 hrs. After filtering the catalyst, distilling off the solvent gave 4-(2-aminophenethyl)-2,6-diisopropylphenol (1.0 g, 84%) as a viscous oil.

5 ¹H-NMR (δ ppm, CDCl₃) 7.02-7.06(m, 2H), 6.83(s, 2H), 6.70-6.77(m, 1H), 6.65(d, J=7Hz, 1H), 4.67(s, 1H), 3.43(bs, 2H), 3.08-3.18(m, 2H), 2.73-2.87(m, 4H), 1.24(s, 6H), 1.22(s, 6H)

Reference Example 3

10 4-(2-Aminostyryl)-2,6-di-tert-butylphenol



To a solution of 2,6-di-tert-butyl-4-(2-nitrostyryl)phenol (1.1 g, 3.1 mmol) in methanol (15 ml) was added water (4 ml), conc. hydrochloric acid (0.2 ml) and iron powder (1.7 g, 30 mmol) and the mixture was heated under reflux for 5 hrs. After filtration, followed by extraction with ethyl acetate and water, the extract was washed with water, dried over MgSO₄ and concentrated. Purification of the residue by a silica gel column chromatography followed by recrystallization from hexane afforded 4-(2-aminostyryl)-2,6-di-tert-butylphenol (0.70 g, 70%).

30 ¹H-NMR (δ ppm, CDCl₃) 7.36-7.38(m, 1H), 7.34(s, 2H), 7.06-7.10(m, 1H), 6.91-7.10(m, 2H), 6.78-6.82(m, 1H), 6.70-6.72(m, 1H), 5.29(s, 1H), 3.79(s, 2H), 1.47(s, 18H)

35 Pharmacological Test

1. ACAT inhibitory activity

The enzyme preparation, ACAT was prepared from liver microsome fractions of male rabbits according to the method of E. E. Largis et al. (Journal of Lipid Research, Vol. 30, pages 681-690, 1989). The activity was calculated by assaying the amount of the labelled cholestryl esters formed from [1-¹⁴C]oleoyl-CoA and endogenous cholesterol according to the method of Kazuichi NATORI et al. (Japan J. Pharmacol., Vol. 42, pages 517-523, 1986).

The result is shown in Table 1, in which percent inhibition of the formation of the labelled cholestryl esters with a compound added at 10⁻⁷M is indicated as index for the ACAT inhibitory activity.

45 The data reveals that the compounds of the invention have a superior ACAT inhibitory activity.

2. Antioxidative activity

50 Human LDL was incubated in the presence of cupric sulfate (5 x 10⁻⁸M) and in the presence or absence of a compound (10⁻⁵M) for 5 hrs. After the incubation, the peroxidation of low-density lipoproteins (LDL) is evaluated by the formation of malondialdehyde (MDA), which is a sort of lipid peroxides according to the method of Simon J. T. Mao et al. (J. Med. Chem., Vol. 34, pages 298-302, 1991). Activity of the compound is shown by percent inhibition of the MDA formation as compared with control. The result is shown in Table 1. The data indicates that the compounds of the invention significantly lower the formation of the lipid peroxide (MDA).

3. Cholesterol-lowering activity

55 Sprague-Dawley male rats were given a powdery feed containing 1% cholesterol and 0.5% cholic acid in an amount of 15 g per day per animal for 3 days to produce hypercholesteremic rats. Four days later, a compound suspended in 0.5% methylcellulose was administered orally at a dose of 30 mg/kg. Blood was drawn prior to and 5 hrs after the administration of the compound, for which the plasma cholesterol level

was measured using a commercially available assay kit (Cholesterol E Test Wako, Wako Junyaku K.K.).
The result is shown in Table 2.

The data shows that the compounds of the invention significantly reduce blood cholesterol level.

5

Table 1

	<u>Compounds of Example</u>	<u>ACAT Inhibition (%)</u>	<u>Antioxidant Activity (%)</u>
10	1	83	94
	4	95	98
15	5	89	100
	6	99	98
20	12	91	94
	13	90	92
25	14	93	98
	15	76	99
30	16	93	95
	17	92	99
35	18	97	97

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	19	100	94
	29	99	95
5	30	84	92
	35	82	94
10	38	71	94
	39	88	87
	40	96	98
15	41	97	99
	42	95	97
20	43	99	99
	44	90	94
	50	88	90
25	52	97	94
	57	89	95
30	69	96	95
	72	97	97
	74	96	95
35	75	88	95
	76	98	96
40	77	96	95
	80	92	96
	83	96	96
45	85	97	94
	90	92	93
50	92	99	96
	97	89	96

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	99	100	95
	108	97	93
5	114	82	98
	115	87	98
10	117	91	97
	124	81	95
	130	99	95
15	140	96	
	141	86	
	146	85	
20	155	94	
	159	97	
25	163	81	
	165	99	
	166	100	
30	167	100	
	168	93	
35	173	95	
	177	98	
	183	91	
40			

Table 2

Compound of Example	Percent Reduction of Cholesterol (%)	
	35	48.4
	83	44.6
	92	79.9
45	105	45.9
	108	71.8
50	130	71.5

55 The pharmaceutical preparations comprising the compounds of the invention are prepared by conventional method in accordance with the following formulations.

<u>Tablets (per tablet)</u>		
5	Compound of Example 6	50 mg
	Hydroxypropylcellulose	2 mg
	Corn starch	10 mg
10	Lactose	100 mg
	Magnesium stearate	3 mg
	Talc	3 mg

<u>Capsules (per capsule)</u>		
15	Compound of Example 17	200 mg
	Starch	8 mg
20	Microcrystalline cellulose	23 mg
	Talc	8 mg
	Magnesium stearate	5 mg

<u>Granules (per divided packet)</u>		
25	Compound of Example 41	1 mg
30	Lactose	99 mg
	Corn starch	50 mg
	Crystalline cellulose	50 mg
35	Hydroxypropylcellulose	10 mg
	Ethanol	9 mg

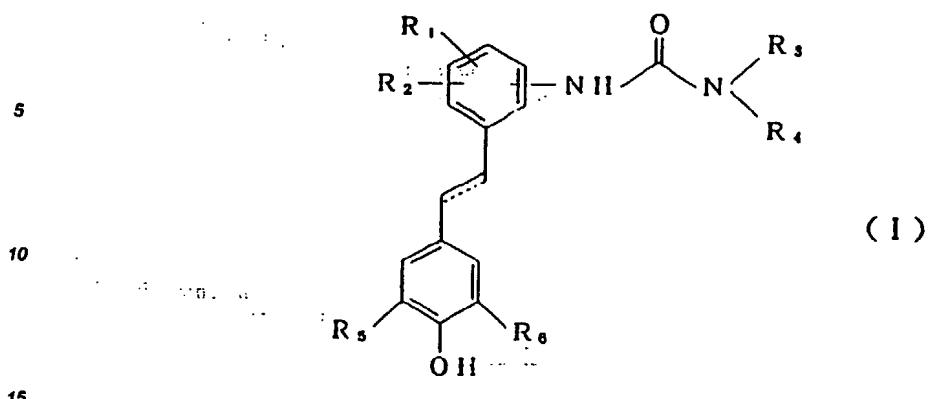
40 **Claims**

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof

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in which:

R₁ and R₂, which may be the same or different, each represents

a hydrogen atom,

20 a halogen atom,

a straight or branched (C₁-C₆)alkyl group or

a straight or branched (C₁-C₆)alkoxy group,

R₃ and R₄, which may be the same or different, each represents

a hydrogen atom,

25 a straight or branched (C₁-C₁₂)alkyl group,

a straight or branched (C₂-C₂₀)alkenyl group,

a (C₁-C₆)alkoxy(C₁-C₆)alkyl group,

a (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkyl group,

a benzyloxycarbonyl(C₁-C₆)alkyl group in which the alkyl moiety is optionally substituted by phenyl,

30 a N,N-di(C₁-C₆)alkylamino(C₁-C₆)alkyl group,

a N-(C₁-C₆)alkyl-N-benzylamino(C₁-C₆)alkyl group,

a (C₁-C₆)alkylthio(C₁-C₆)alkyl group,

an oxo(C₁-C₆)alkyl group,

a hydroxy(C₁-C₆)alkyl group,

35 a dihydroxy(C₁-C₆)alkyl group,

a cyclo(C₃-C₁₅)alkyl group,

a cyclo(C₃-C₈)alkyl(C₁-C₆)alkyl group,

a dicyclo(C₃-C₈)alkyl(C₁-C₆)alkyl group,

a bicyclo(C₆-C₉)alkyl group,

40 a tricyclo(C₉-C₁₂)alkyl group,

in which in all cases the cycloalkyl group or the cycloalkyl moiety is optionally substituted by one or two substituents selected from the group consisting of (C₁-C₆)alkyl, hydroxy, amino, acetoxy, acetamido, phenyl, benzyloxy, dimethylaminophenyl, and methylenedioxophenyl, which may be further fused with a benzene ring.

45 an aryl group,

an aryl(C₁-C₆)alkyl group,

a diaryl(C₁-C₆)alkyl group,

50 in which in all cases the aryl group or the aryl moiety is optionally substituted by one, two or three substituents selected from the group consisting of (C₁-C₆)alkyl, (C₁-C₆)alkyloxy, halogen, nitro, hydroxy, amino, dimethylamino, methylenedioxy, and pyrrolidinyl,

a heterocyclic group or

a heterocyclic group attached to a (C₁-C₆)alkylene chain,

55 in which in all cases the heterocyclic group represents a saturated or unsaturated, 5 to 8 membered ring monocyclic or bicyclic, heterocyclic group containing 1 to 3 heteroatoms selected from the group consisting of S, O and N, and the heterocyclic group is optionally substituted by one or two substituents selected from the group consisting of acetyl, hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkyloxy, cyclo(C₃-C₈)alkyl, cyclo(C₃-C₈)alkyl(C₃-C₁₀)alkyl, pyridyl(C₁-C₆)alkyl, phenyl, phenyl(C₁-C₆)alkyl, diphenyl(C₁-C₆)alkyl, and phenylpiperazinyl, the phenyl group or the phenyl moiety being optionally substituted by one

or two substituents selected from the group consisting of halogen, hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, cyano, diethylamino and trifluoromethyl, which may be further fused with a benzene ring, and further R₃ and R₄, together with the nitrogen atom to which they are attached, may form a saturated or unsaturated heterocyclic group,

5 in which the heterocyclic group represents a 5 to 8 membered ring monocyclic or bicyclic, heterocyclic group or a group derived from a heterocyclic spiro compound, which may contain one or two heteroatoms selected from the group consisting of S, O or N, the heterocyclic group being optionally substituted by one or two substituents selected from the group consisting of (C₁-C₆)alkyl, hydroxy, hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, acetoxy(C₁-C₆)alkyl, (C₁-C₆)alkylcarbonyl, (C₁-C₆)alkoxycarbonyl, 10 amino, tosyl, phenyl, halogenophenyl, (C₁-C₆)alkoxypyhenyl, phenyl(C₁-C₆)alkyl, benzyloxy, benzyloxy(C₁-C₆)alkyl, tolyl, xylyl, benzoyl, methylenedioxypyhenyl(C₁-C₆)alkyl, pyridyl, pyridylcarbonyl, piperidyl, pyrrolidinyl(C₁-C₆)alkyl and pyrrolidinylcarbonyl(C₁-C₆)alkyl, which may be further fused with a benzene ring, in which in all cases the alkyl and alkoxy moieties may be either straight or branched, with the proviso that both R₃ and R₄ do not represent a hydrogen atom at the same time;

15 R₅ and R₆, which may be the same or different, each represents a straight or branched (C₁-C₆)alkyl group; and the line



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represents -CH₂CH₂- or -CH=CH-.

2. A compound of claim 1 wherein R₃ and R₄, which may be the same or different, each represents a hydrogen atom,

25 a straight or branched (C₁-C₁₀)alkyl group,

a straight or branched (C₃-C₁₇)alkenyl group,

a (C₁-C₄)alkoxy(C₁-C₄)alkyl group,

a (C₁-C₄)alkoxycarbonyl(C₁-C₄)alkyl group,

30 a benzyloxy carbonyl(C₁-C₄)alkyl group in which the alkyl moiety is optionally substituted by phenyl,

a (C₁-C₄)alkylthio(C₁-C₄)alkyl group, a cyclo(C₃-C₁₂)alkyl group or a cyclo(C₅-C₇)alkyl(C₁-C₄)alkyl group in which the cycloalkyl group or the cycloalkyl moiety is optionally monosubstituted by a substituent selected from the group consisting of (C₁-C₄)alkyl, hydroxy, amino, acetoxy, acetamide, phenyl, benzyloxy, dimethylaminophenyl and methylenedioxypyhenyl, or the cycloalkyl group or the cycloalkyl moiety is optionally fused with a benzene ring;

35 a dicyclohexyl(C₁-C₄)alkyl group, a bicyclooctyl group, an adamantyl group, a phenyl group optionally substituted by (C₁-C₄)alkyl or hexyloxy, a naphthyl group, an anthryl group, a phenyl(C₁-C₄)alkyl group in which the phenyl moiety is optionally substituted by one or two substituents selected from the group consisting of (C₁-C₄)alkyl, (C₁-C₄)alkyloxy, halogen, nitro, hydroxy, amino, dimethylamino, methylenedioxo and pyrrolidinyl;

40 a diphenyl(C₁-C₄)alkyl group, a heterocyclic group or a heterocyclic group attached to a (C₁-C₄)alkylene chain in which the heterocyclic group represents a saturated or unsaturated, 5 or 6 membered ring monocyclic or bicyclic, heterocyclic group containing 1 or 2 nitrogen atoms and the heterocyclic group is optionally substituted by one or two substituents selected from the group consisting of acetyl, hydroxy, (C₁-C₆)alkyl, cyclohexyl, pyridyl(C₁-C₄)alkyl, phenyl(C₁-C₄)alkyl or diphenyl(C₁-C₄)alkyl in which the phenyl moiety is optionally substituted by one or two substituents selected from the group consisting of halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, cyano, diethylamino and trifluoromethyl, and phenylpiperazinyl, which may be further fused with a benzene ring;

45 and further R₃ and R₄, together with the nitrogen atom to which they are attached may form a saturated or unsaturated heterocyclic ring, in which the heterocyclic group represents a 5 to 7 membered ring monocyclic or bicyclic, heterocyclic group or a group derived from a heterocyclic spiro compound, which contain one or two nitrogen atoms, the heterocyclic group being optionally substituted by one or two substituents selected from the group consisting of (C₁-C₄)alkyl, hydroxy(C₁-C₄)alkyl, acetoxy(C₁-C₄)alkyl, (C₁-C₆)alkylcarbonyl, (C₁-C₄)alkoxycarbonyl, tosyl, phenyl, phenyl(C₁-C₄)alkyl, benzyloxy, benzyloxy(C₁-C₄)alkyl, benzoyl, methylenedioxypyhenyl(C₁-C₄)alkyl, pyridylcarbonyl, piperidyl and pyrrolidinylcarbonyl(C₁-C₄)alkyl.

55

5. A compound of claim 2 wherein R₃ and R₄, which may be the same or different, each represents a hy-

drogen atom, a straight or branched (C₁-C₇)alkyl group, a cyclo(C₄-C₈)alkyl group, a heterocyclic group or a heterocyclic group attached to a (C₁-C₄)alkylene chain in which the heterocyclic group represents a saturated or unsaturated, 5 or 6 membered ring monocyclic or bicyclic, heterocyclic group containing one nitrogen atom and the heterocyclic group is optionally substituted by one or two substituents selected from the group consisting of methyl, ethyl, cyclohexyl, pyridylmethyl, and phenyl(C₁-C₃)alkyl in which the phenyl moiety being optionally substituted by one or two substituents selected from the group consisting of halogen, methoxy, cyano, dimethylamino and trifluoromethyl, which may be further fused with a benzene ring.

10 4. A compound of claim 3 wherein R₃ and R₄, which may be the same or different, each represents a hydrogen atom, a straight or branched (C₁-C₄)alkyl group, cyclohexyl, cycloheptyl, pyrrolidinyl or piperidyl, the latter two heterocyclic groups being optionally substituted by one or two substituents selected from the group consisting of methyl, ethyl, cyclohexyl, pyridylmethyl, and phenyl(C₁-C₃)alkyl in which the phenyl moiety being optionally substituted by one or two substituents selected from the group consisting of halogen, methoxy, cyano, diethylamino and trifluoromethyl, which may be further fused with a benzene ring.

15 5. A compound of claim 2 wherein R₃ and R₄, together with the nitrogen atom to which they are attached, may form a saturated or unsaturated heterocyclic ring, in which the heterocyclic group represents a 5 or 6 membered ring monocyclic or bicyclic, heterocyclic group which contain one or two nitrogen atoms, the heterocyclic group being optionally substituted by one or two substituents selected from the group consisting of methyl, hydroxyethyl, acetoxyethyl, pentylcarbonyl, ethoxycarbonyl, tosyl, phenyl, benzyl, benzylxyloxy, benzylxyethyl, benzoyl, methylenedioxybenzyl, pyridylcarbonyl and piperidyl, which may be further fused with a benzene ring.

20 6. A compound of formula (I) as defined in claim 1 specifically identified herein or a pharmaceutically acceptable salt thereof.

25 7. A compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any of claims 1 to 6 for use in therapy.

30 8. A compound as claimed in claim 7 for use in ACAT inhibition.

9. A pharmaceutical composition comprising as an active ingredient a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any of claims 1 to 6 and a pharmaceutically acceptable carrier and/or excipient.

35 10. Use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any of claims 1 to 6 in the manufacture of a medicament for the prophylaxis and treatment of hypercholesterolemia and atherosclerosis.

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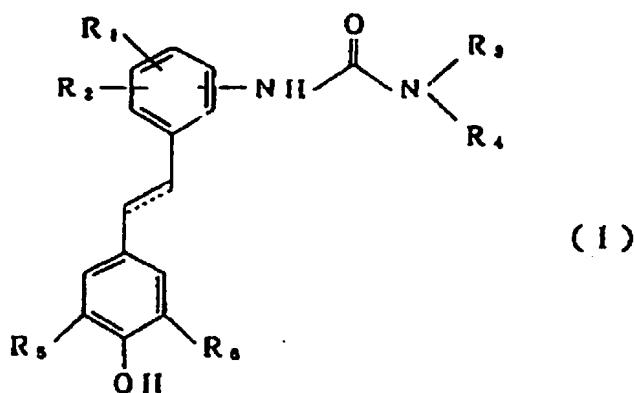
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EP 0 625 507 A3

㉓ Urea derivatives and their use as acat inhibitors.

㉔ Urea derivatives of formula (I)



wherein the valuable groups are as defined in the specification, which possess both an ACAT inhibitory activity and an antidiabetic activity. Those derivatives are useful in the prophylaxis and treatment of hypercholesterolemia and atherosclerosis.

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DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
Y	EP-A-0 370 740 (WELLCOME) * whole document *	1-10	C07C275/32 A61K31/17 C07C275/34 C07D307/52 C07D295/13 C07D211/58 C07D317/58 C07D295/215 C07D211/16 C07D213/40 C07D295/20 C07D295/12
Y	EP-A-0 527 458 (BOEHRINGER MANNHEIM) * page 2, line 8 - line 29; claims; examples *	1-10	
A	EP-A-0 344 425 (WARNER LAMBERT) * claims; examples *	1-10	
D,A	EP-A-0 450 660 (WELLCOME) * whole document *	1-10	
D,A	EP-A-0 477 778 (EISAI CO. LTD.) * claims; examples *	1-10	
The present search report has been drawn up for all claims			TECHNICAL FIELDS SEARCHED (Int.Cl.)
			C07C C07D
(Int.Cl.)			
Place of search		Date of compilation of the search	Examiner
THE HAGUE		5 October 1994	Helps, I
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